*The Banting Memorial Lecture 1960**

Childhood Diabetes

Its Course, and Influence on the Second and Third Generations

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INTRODUCTION

Thank you for honoring me by inviting me to give the 1960 Banting Memorial Lecture. The subject, childhood diabetes, remains as important a tribute to the discoverers of insulin as it was in 1922. The world's one million individuals surviving childhood diabetes, and their numerous offspring, exist today only because of their discovery. The dramatic subjective change from the pre-insulin to the insulin era has been described in a letter written to Dr. Elliott Joslin by our oldest diabetic child, who in January 1960 celebrated his sixtieth birthday. He was the first patient in the United States to receive insulin. He writes, "I remember so vividly . . . that the first treatment seemed to have little effect. Dr. Banting came right over with some insulin in his pocket and stayed overnight and they had me sugar-free in twenty-four hours, for the first time in many years! And of course I remember too how I sat in a chair and read in comfort for the first time, the pain that had been so incessant in my feet having gone. After we were married—1927—my wife and I used to camp in Canada one hundred miles or so north of Toronto and on the way home we used to look up Fred Banting, always working quietly in a laboratory at the University of Toronto. Part of me certainly went away when Fred Banting was lost in Newfoundland! My parents arranged a dinner for him with George Eastman, who was anxious to persuade him to come to Rochester and work at the new medical school here. When Banting told Eastman his first loyalty was to Canada, Eastman turned to my father and said, 'There's a young man I admire, he has backbone.' "

MATERIAL

Juvenile diabetes is defined in this discussion as the form of the disease which has its onset under age fifteen. Between 1898 and 1960, 4,774 childhood cases have been enrolled in the Joslin Clinic. Currently 478 of the total number have survived more than thirty years of diabetes. The magnitude of their problems is great, indeed. As perplexing questions are answered, others demand investigation. Genetically, structurally, functionally and psychologically these young diabetics have influenced their new second and beginning third generation.

ONSET—NATURAL COURSE

Juvenile diabetes follows a definite natural course, characterized by an acute onset, often with rapid progression to diabetic coma. A triad is observed at onset. Insulin-like activity of the blood increases to levels above the normal, hypertrophy and hyperplasia of the islets of Langerhans are demonstrable, and insulin may be extracted from the pancreas in only slightly subnormal amounts.

REMISSION—INTENSIFICATION TO TOTAL DIABETES

Consequently, and in a relatively short period of time after the initiation of antidiabetic treatment, remissions occur. Insulin requirements drop; responsiveness to sulfonylurea and biguanide is evident. In varying lengths of time intensification of diabetes follows until eventually total diabetes is manifest. The factors implicated in the intensification of juvenile diabetes include linear growth, puberty, infections and both hyper- and hypoglycemia.

Total diabetes is identified by the occurrence of nocturnal hyperglycemia and consequent increased requirements for insulin, by the failure of responsiveness to sulfonylurea and to biguanide alone. The relative rate of its development is rapid. Some 10 per cent demonstrate it at the time of diagnosis. By the end of the first year of diabetes, 40 per cent; by the end of the second year, 60 per cent; the third year, 70 per cent; and by the fifth year, 90 per cent show the totally diabetic state.

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Subsequently the percentage increases to 94. Some 5 or 6 per cent progress slowly or perhaps not at all. The triad changes. There is no longer insulin-like activity in the blood. After the fifth year of diabetes pancreatic islets are few, eventually becoming atrophic and agranular. Little or no insulin is extractable from the pancreas.

SOMATIC GROWTH

Although growth and development, the normal functions of childhood and youth, may be affected adversely by diabetes, satisfactory end results are achieved.

In our clinical exploration of the trends of growth and in the experimental observations upon the administration or removal of growth hormone, interrelationships are apparent. That in certain species the administration of growth hormone induces diabetes and that hypophysectomy relieves it, is well known. Of more recent knowledge is its antagonistic and/or inhibitory influence upon insulin activity and that in the rat long-acting PZI was found to influence growth (weight, fat, muscle, protein metabolism) favorably after hypophysectomy.

CLINICAL OBSERVATIONS

In the remote prediabetic state, at birth, there is no evidence of overgrowth. The birth weight of juvenile diabetics and their presently nondiabetic siblings average 3,090 and 3,150 gm. respectively. But accelerated growth has characterized the immediate prediabetic period. Throughout the years average height at onset has been found to be twelve months in advance of chronological age. The bone age was eighteen months, the dental age twelve months advanced and the first components of puberty appear earlier than in nondiabetic controls.

A potential deficit of growth exists, however. Between 1922 and 1936 failure of linear growth characterized juvenile diabetics. This unfavorable effect is still apparent in the 478 thirty-year survivors, 13 per cent of whom are still or had been 10 to 30 per cent below standard average height. Failure of linear growth became manifest in the fifth year of the duration of diabetes. It affected more boys than girls. It was associated with varying degrees of overweight which amounted to obesity in nearly 20 per cent of the boys and 40 per cent of the girls. Hepatomegaly was found universally. The enlarged liver was infiltrated with fat.

With the discovery and appropriate use of long- and intermediate-acting insulins the failure of growth associated infantilism and hepatomegaly have been eliminated. The same hormone, insulin, administered parenterally but in two forms differing in their time action, affected growth differently. With quicker availability but shorter duration of action the lipogenic, fat storage, effect was evident in the obese diabetic dwarf. With delayed availability but prolonged action the total anabolic effect has been demonstrated. As in the hypophysectomized rat the permissive role of insulin upon growth is shown.

The superior level of height characteristic of juveniles at onset may be lost but satisfactory average rates of growth follow. In 1959 a comparison of the height, weight, age relationship of ninety-four diabetics was made with their seventy-four nondiabetic siblings. Between the ages of five and sixteen the averages per each year were almost identical. Plotted on the Wetzel grid they approximated each other closely in channels of growth and auxodrome levels.

The effect of linear growth upon diabetes after onset may be seen in the period of intensification. Compared with adolescent girls the insulin requirement of adolescent boys is disproportionately great. This occurs concomitantly with their greater spurt of growth. Thus, clinical and experimental observations corroborate each other in respect to growth and appear to implicate a growth hormone influence in juvenile diabetics.

DEVELOPMENT

An effect of diabetes upon puberty development and of puberty upon the course of diabetes are also apparent. Thus, the peak for the age of onset of juvenile diabetes is prepuberty, at eleven years of age—ten for girls with their earlier development and thirteen for boys with their later development.

Intensification of diabetes may coincide with puberty. Using menarche as the most significant parameter of development, prediabetes is associated with the earliest reported age. This is shown in diabetics whose onset began above the age of eighteen. Latest menarche is reported for those whose diabetes starts under eleven. This latter delay has no apparent effect upon fertility. Sterility is rare in the young diabetic male and even more exceptional in the female surviving childhood diabetes.

The large family size characteristic of prediabetes is equally characteristic of long-term young diabetic males. The 225 male juvenile thirty-year survivors had 338 children. This number is 72 per cent of all the children of the thirty-year survivors. Fifty (22 per cent) were supporting families of more than two children. Nine was the largest number of children. The father, Case No.

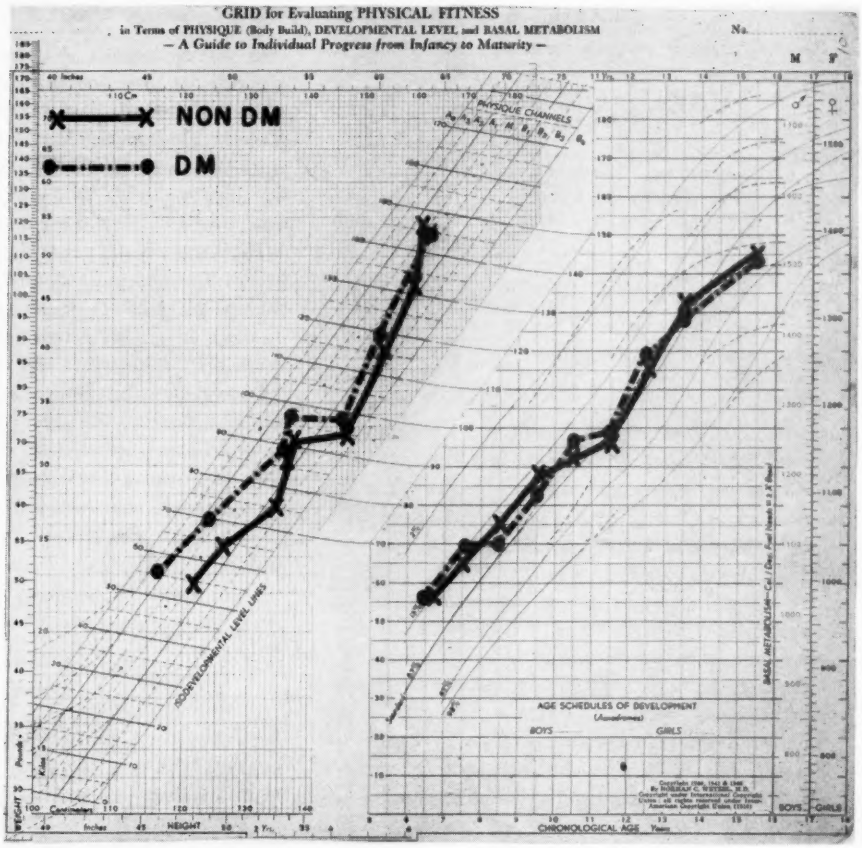

FIG. 1. Comparison of height, weight, age relationship of diabetic girls and their nondiabetic siblings.

6,664, developed diabetes in 1924 at the age of four.

In our experience, no diabetic girl surviving typical childhood diabetes has a family of comparable size. The 253 female juvenile thirty-year survivors had only 129 surviving children, or 28 per cent of the children of thirty-year survivors. Comparisons of viable salvage rates in adult and juvenile onset diabetes show the greater fetal hazard in the younger onset group. For these patients who had clinical diabetes with onset above age twenty (278 cases), the viable survival (after twenty-eight weeks) was 92 per cent. For 697 pregnancies in 347 juvenile patients with identical type management, viable survival was 81 per cent. Previable losses were 10 per cent for the former, 16 per cent for the latter group. Thus the diabetic girl, in contrast to the diabetic boy and the maturity onset diabetic female, has a poorer chance for reproducing surviving children. At the time of her first pregnancy she has had total diabetes of appreciable duration, often with vascular sequelae. Neither malignant retinopathy nor nephropathy contraindicates pregnancy in our patients. In January 1960 two blind diabetics with proliferating retinopathy and nephropathy delivered three surviving infants. As renal function diminishes, mothers survive but fetal losses increase. In addition to her metabolic and vascular lesions, her endocrine balance is disturbed. She lacks endogenous insulin, estrogen and progesterone. Her intensified diabetic state becomes even more unstable and more difficult to control. She develops ketoacidosis easily, retains sodium, overproduces amniotic fluid and is prevented from developing pre-eclampsia only with meticulous care. She requires ever increasing doses of insulin, sodium restriction and diuretics. Added protection is achieved through replacement of deficient progesterone and estrogen. The importance of the latter is suggested by the in vitro experiments of Villee indicating that in estrogen-sensitive tissues estradiol activates a transhydrogenase which permits reshuttling of

TABLE 1

Renal function in pregnancy complicating diabetes

Class	Patients No.	Observations No.	G.F.R./1.73M²(ml./min.) Mean ± S.D.	Viable pregs. completed June 1, 1960 No.	L.B. No.
A	2	7	107±20	2	2
B	17	80	95±36	14	13
C	20	52	91±30	13	13
D	46	154	85±21	24	19
F	3	17	57±17	3	3
	88	310		56	50

TABLE 2

Age at onset

Age at onset	Thirty-year duration juvenile diabetics Males	Females	Total
<1	2	0	2
1	12	11	23
2	11	12	23
3	18	19	37
4	15	14	29
5	21	29	50
6	15	20	35
7	15	17	32
8	14	16	30
9	15	21	36
10	13	22	35
11	15	19	34
12	21	26	47
13	16	10	26
14	19	16	35
15	3	1	4
	225	253	478

TABLE 3

Duration of diabetes

Duration (years)	Thirty-year duration juvenile diabetes Males	Females	Total
30-34.9	147	180	327
35-39.9	65	67	132
40-44.9	12	6	18
45+	1	0	1
	225	253	478

the reduced phosphopyridine nucleotides, thereby increasing the amount of biologic energy available through high-energy phosphate bonds and favoring normal rates of tissue synthesis.

COMPLICATIONS

In varying degrees of intensity and frequency, juvenile patients have developed coma, infections, neuropathies and vascular changes. In order to evaluate these sequelae, the 478 patients surviving thirty to forty-six years of juvenile diabetes have been analyzed separately. On Jan. 1, 1960, 75 per cent were living, 11 per cent were dead and 14 per cent were untraced.

Keto-acidosis and coma. That the incidence of severe ketosis has been great in this group is compatible with the malignant nature of their totally diabetic state. One or more attacks were reported in 61 per cent, but no death after thirty years was due to this cause.

Neuropathy. Neuropathies eventually developed in half the number. The most common forms were those with the best prognosis for recovery, namely, peripheral neuritis 48 per cent and gastroenteropathies 20 per cent. Tabetic bladders occurred in 3 per cent; involvement of the cranial nerves and of joints less than 1 per cent each.

TABLE 4

Complications among 478 juvenile thirty-year survivors

	Neuropathy Total (478) per cent	Living (422) per cent	Fatal (56) per cent
Peripheral	48.0	44.0	84.0
Gastrointestinal	20.0	19.0	23.0
Bladder	3.0	3.0	4.0
Joint	0.4	0.5	—
Cranial	0.8	0.5	8.0

Infections. Of greater significance and possibly somewhat interrelated were infections and vascular lesions. Of the four common sites of infection—skin, urinary tract, lung and bone—infections of the skin were the most frequent (54 per cent); tuberculosis and osteomyelitis least frequent, in 6 and 5 per cent respectively, with urinary tract infections common in 28 per cent. The immediately lethal aspects of coma and sepsis being resolved, vascular damage remains the challenging problem.

TABLE 5

Complications among 478 juvenile thirty-year survivors

	Infections Total per cent	Living per cent	Fatal per cent
Skin	55	54	62
Urinary tract	28	26	41
Bone	5	4	12
Tuberculosis	6	6	12

What part is preventable? What part is remediable?

The data compiled from juvenile patients are pertinent to the evaluation of the common concepts regarding the nature of diabetic angiopathy as an inherited trait, a component, a complication of diabetes, or any combination of these. All three methods for studying the inception of vascular changes indicate its early onset. The three methods include percutaneous renal biopsy with electron microscopy, direct examination of the vasomotor responses of the micro vessels of the bulbar conjunctiva with photographic record and, finally, observations in short-term cases by standard pathological technics.

Percutaneous renal biopsy has revealed involvement of the glomerular capillaries in early, first-year duration, diabetes of the adult type. The degree of the thickening of the basement membrane was significant. Diffuse and later nodular lesions develop. The nodular form appeared to develop not as a deposition but from complex folding and formation of anastomosing trabeculae of basement membrane-like material. Such studies, to my knowledge, actually have not been done in early childhood cases of diabetes except in the presence of acute renal disease.

The micro vessels of the bulbar conjunctiva, however, have been examined at the time of the diagnosis of juvenile diabetes. They have shown venular dilatation with erythrocyte aggregation and micro thrombi. Long-term juvenile diabetics showed, in addition, arteriolar constriction with aggregation of erythrocytes and micro thrombi.

The standard light technic also has shown the early appearance and all inclusiveness of the vascular lesions. The shortest duration of diabetes of the juvenile type with arteriosclerosis reported by Warren and LeCompte was one week. When the average survival was 1.2 years, 25 per cent showed atherosclerosis; when the average survival was 5.5 years, 71 per cent; later, with an average survival of fourteen years, 83 per cent showed vascular lesions.

The clinical recognition of vascular lesions in the juvenile patient, however, was exceptional in the first five years of duration, 1 per cent; rare even in the first ten years, 2.5 per cent. By fifteen years, however, 20 per cent; by twenty years 60 per cent; and by thirty years 90 per cent show vascular damage. No lesion has been recognized clinically under ten years of age, in 7 per cent by twenty years of age and in 63 per cent by thirty years of age. The order of appearance of the lesions in juvenile diabetes consists, first, of retinopathy (dilated vein, micro-aneurysm), then calcified arteries, then proteinuria and later hypertension.

TABLE 6

Complications in 478 thirty-year survivors

	Angiopathy		
	Total per cent	Living per cent	Fatal per cent
Retinopathy	90	90	90
Proliferating	33	30	59
Calcified Arteries			
Legs	83	82	90
Pelvis	36	34	55
Abdominal aorta	16	14	26
Thoracic aorta	3	2	7
Nephropathy (proteinuria)	42	34	80
Hypertension	43	37	85

In the thirty-year survivors, two trends for the clinical course of angiopathy appear. In the one, more commonly seen in females and those with diabetes onset under ten years, were characteristic retinopathy, dilated venules, preretinal and vitreous hemorrhages, nephropathy and co-existing azotemia. More commonly seen in males and those with onset after ten years are hypertension, extensive involvement of medium-sized vessels showing calcification in X ray, minimal evidence of nephropathy and of retinopathy but eventual inclusion of coronary vessels and of the myocardium. In these two different clinical courses there is a suggested parallel to the patterns described by Ditzel in the bulbar conjunctiva, venular dilatation progressing toward retinopathy and nephropathy and arteriolar constriction progressing toward calcification and hypertension. The involvement of the vasa vasorum and nerva vasorum unifies this concept.

Better degrees of diabetes control are characterized by infrequent and nonmalignant and delayed involvement of the vascular system. Poorer degrees of control are characterized by frequent, malignant and early vascular involvement. This has been reported universally by the clinicians who have been privileged to follow the same juvenile patients serially over many years. The different degrees of diabetes characteristic of adult onset cases do not occur in juvenile onset patients, almost all of whom show the totally diabetic state and who therefore give better indices of the effect of relatively good and poor control of the disease.

Rapid development of malignant lesions coincides with the maximum periods of poor management. Our most striking example of this was seen in M.N., Case 42,387, who in the sixth year of her diabetes at age seventeen was admitted to the New England Deaconess Hospital with diabetic coma complicated by staphylo-

coccus pneumonia. She recovered from keto-acidosis but progressed rapidly into renal acidosis. Proteus pyelonephritis followed. Her final recovery was achieved by dialysis. The renal biopsy showed acute tubular necrosis and thickening of the basement membrane with both PAS and electron microscopy. In the eighth week after recovery, her retinae, normal when she was admitted to the hospital, showed renal and advanced diabetic retinopathy which included patches of neovascularization in both eyes. (This patient will be reported in detail by Rees and Spiro.)

The opportunity to study the retinae of young diabetics serially at weekly intervals has re-emphasized the potentially reversible character of some and the stationary or progressive nature of other vascular lesions. Rapid reversal of venular dilatation, micro-aneurysms, hemorrhages and waxy exudate may occur. Preretinal and vitreous hemorrhages resorb slowly. Proteinuria and hypertension may be transitory, stationary or progressive. Calcified deposits, retinal scars and new blood vessels may remain stationary or progress. Dissociation of the degree of retinal and renal involvement may occur also.

In the 478 thirty-year survivors the relative frequency of sequelae with loss of function is as follows: Retinopathy progressed to blindness in 8 per cent; hypertension progressed to cerebrovascular accidents in 4 per cent, to myocardial infarction in 19 per cent; calcified arteries progressed to gangrene in 3 per cent. Striking differences are seen in surviving and fatal cases. Remedial programs designed to prevent the accelerated development of angiopathy include chemical control of diabetes and search for latent infections, especially those of the urinary tract. For the female it may be possible that the improved renal function of pregnancy and its management can be utilized as a part of their protective program.

Iatrogenic production of vascular damage has been suggested. Acceleration of nephropathy has been described by Fanconi, who reported his experience with low protein diets. Although he maintained juvenile patients in positive nitrogen balance, they died of nephropathy before the twentieth year of their diabetes.

Protamine Zinc Insulin and NPH insulins have been implicated in the production of vascular lesions but juvenile diabetics treated with Regular Insulin only developed nephropathy, retinopathy, calcified arteries and hypertension. Such juvenile patients seen prior to 1936 showed the clinical picture recognized today as that of intercapillary glomerulosclerosis, died of renal failure, but at autopsy these lesions were classified as nephrosis. The implication of exogenous insulin itself in the production of retinopathy and nephropathy cannot be answered by this group because of the short survival of childhood diabetics prior to 1922.

Management. Enough time has elapsed to establish the fact that oral substitutes do not replace insulin therapy in childhood. Few juvenile diabetics are affected by them alone after a few months of duration. The remission phase has not been significantly prolonged.

Physiological control is achieved best with intermediate insulins in mixtures and split-dose schedule. Patients developing reactions without warning respond to the combination of insulin and biguanide. The mixture of Semi- and Ultralente in this program may eliminate a second injection in twenty-four hours.

Dietary programs facilitate physiological control whether it is the normal partition of carbohydrate, protein and fat, 50 per cent, 15 per cent, 35 per cent, the reverse, or one such as 40 per cent, 20 per cent, 40 per cent, which we employ. The difficulty of achieving ideal control may be explained on the basis of their totally diabetic state, antibody formation and especially antagonism to insulin.

Unusual cases were found in our long-term group. This included two cured cases thought to have typical juvenile diabetes but actually having adrenal tumors. Six patients have been followed for thirty or more years after positive glucose tolerance tests. They are well and have not developed clinical diabetes or vascular lesions.

Attempts to alter diabetes. Attempts have been made to alter diabetes course and outcome. The first serious attempt was the method of Brush. By the use of overinsulinization he hoped to prolong remissions. Time has shown that children so treated followed the natural course of diabetes described.

Houssay and his associates have found that estrogen, thyroxin, cortisone, hydrocortisone and growth hormone combined with insulin reverse experimentally induced diabetes and produce islet hypertrophy and hyperplasia. The experience of our former juveniles who received female sex hormones in pregnancy was encouraging. Fifty per cent maintained a 50 per cent reduction of insulin and 20 per cent a 75 per cent reduction over their stable prepregnancy insulin requirement. An attempt to duplicate this experience was made. Seventy-five juveniles in remissions were each treated in groups of twenty-five with insulin and cortisone, insulin and thyroxin, insulin and sulfonylurea. With the exception of one, Case No. 44,053, treated with insulin and cortisone, all followed the natural course of juvenile diabetes. Case No. 44,053, thirteen years of age at onset,

required no insulin in the seventh year of his diabetes.

Transplants of pancreatic tissue of immature cell type have been attempted in seven of our juveniles. Five times the source was fetal tissue, twice islet cell tumor. The islet tumor cells were transplanted, after culture, in millipore chambers. The five patients with fetal transplants behaved no better than the patients described as having had estrogen. The patients with islet cell transplants showed a 50 per cent lowering of insulin requirement which has persisted for six months. Examination of the tissue twelve weeks after insertion showed fibrous tissue without islets.

Subsequent careers of our long-term patients are encouraging. Forty per cent attended college, 9 per cent graduate school, and 34 per cent entered professions as compared with 6 per cent expected in the general population.

Psychological problems occur because of the nature of diabetes and its necessary treatment. Any illness involving so many organs and vital structures is difficult for the child to understand. Insulin reactions producing a total loss of control with emphasis on food, urine, injections, revive early childhood struggles. The normal problems of adolescence are exaggerated in the child with chronic disease. Fear of death is more common in their childhood than is normal. At later ages feelings of physical inadequacy occur concomitantly with the awareness of serious sequelae. Nine per cent of our long-term patients were disturbed seriously enough to attempt suicide or require temporary institutional care.

Medal cases. Sixteen of the thirty-year survivors had been awarded Victory Medals for perfect physical status after twenty-five years of diabetes. This is 18 per cent of all the Medal cases.

Expectation of life. Four of the 478 juveniles surviving thirty years reached their expected life span of fifty-five years of age for individuals born before 1930, and 92 per cent exceeded the two-thirds life span prediction for diabetics. In the thirty-year group nephropathy was replaced by cardiovascular disease as their chief cause of death.

SECOND GENERATION

Of greatest concern in our evaluation of the influence of juvenile diabetes upon the second and third generation is the transmission of diabetes, the incidence of congenital anomalies, the deviation of patterns of growth, deficits of the central nervous system, involvement of the vascular tree, and the occurrence of the possible emotional problems related to parental diabetes.

A comparison of the two groups, children of diabetic fathers and of diabetic mothers, indicates that juvenile diabetic maternal environment, prenatal, natal and postnatal, has a greater influence upon the second generation than did the diabetic paternal environment.

TABLE 7

Age in 478 juvenile thirty-year survivors

Age Years	Present age			Age at death		
	Male	Female	Total	Male	Female	Total
30-34.9	20	15	35	3	4	7
35-39.9	59	71	130	6	10	16
40-44.9	57	83	140	8	13	21
45-49.9	51	46	97	6	4	10
50-54.9	10	6	16	2	—	2
55-59.9	2	1	3	—	—	—
60-	1	0	1	—	—	—
	200	222	422	25	31	56

TABLE 8

Causes of death in fifty-six thirty-year survivors of diabetes, ages thirty to fifty-five years

Cause of death	No. Pts.	Pts. (per cent)	
Heart	29	52	86
Kidney	17	30	
Cerebral	2	4	
Cancer	2	4	
Others	6	10	

Children of diabetic fathers. Although the relative number of our young diabetic patients producing diabetic children was identical, 4 per cent of the 225 diabetic males and 4 per cent of the 253 long-term diabetic females, the incidence of diabetes in the offspring was 2 per cent for diabetic fathers and 8 per cent for the diabetic mothers. Congenital anomalies were found with equal frequency, but were of less severe degree in the offspring of diabetic fathers. Obesity, edema, embryopathy were not characteristic. Only 1 per cent of the newborn infants of diabetic fathers weighed more than ten pounds at birth. The offspring of the fathers did not show neurological deficits, and although the micro vessels of the bulbar conjunctiva were not examined, they showed none of the other vascular lesions which occurred in the children of diabetic mothers. Their growth trend in the age period of six to sixteen years was not unusual.

The children were not often disturbed emotionally by paternal diabetes. The young diabetic father often showed unusual interest in details of their growth and development.

OFFSPRING OF DIABETIC MOTHERS

Diabetes. The incidence of diabetes in the 129 surviving children of thirty-year duration diabetic girls was 7 per cent, or one child in fourteen; the range of their

ages in the second generation was months to thirty years. Since 12 per cent of these 478 young patients had diabetic parents and 4 per cent diabetic offspring, the concept of the Mendelian recessive transmission is supported again.

Anomalies. The incidence of anomalies in the 556 viable infants of juvenile diabetics in our entire series of obstetrical cases was 9 per cent. The incidence of anomalies was no greater in the offspring in the juvenile than in our adult diabetic population. Since the most common anomalies were those of the heart (3 per cent), the prognosis for survival is becoming increasingly greater. The incidence of congenital heart lesions in juvenile diabetics themselves is 1 per cent.

Potentiality for central nervous system deficits. In the immediate neonatal period the electively premature infant of the diabetic mother often struggles for survival. During the periods of respiratory distress, oxygen deprivation occurs. The influence of this deprivation upon the central nervous system requires further investigation. The school progress of these children appeared to be satisfactory, and the revealed deficit was less than 3 per cent.

TABLE 9

Congenital anomalies in children of diabetic mothers

Site	Per cent	Site	Per cent
Heart	3	G.I. tract	<1
C.N.S.	2	G.U. tract	<1
Bone	2	Lungs	<0.5
Eye	1	Veins	<0.5
Kidney	1	Mongolism	<0.5
Ears	<1		

Transitory complications. The edema and obesity of the newborn are transitory. The latter may represent overnutrition from hyperglycemia or the lipogenic action of insulin. Length and bone development do not exceed normal average at birth. Birth weights were influenced by early delivery dates: 1.0 per cent exceeded ten pounds; 33 per cent were 7-9.9; 66 per cent were less than six pounds.

Embryopathy. The infant of the pre- or clinical diabetic shows islet hypertrophy and hyperplasia as does the erythroblastic infant.

Subsequent growth of children of diabetic mothers. Between the ages of six and sixteen the trend toward gigantism characterizes the child of the young diabetic mother. This accelerated growth influenced height, weight and bone development, but the weight-height relationship of sons was the most striking. The sons of diabetic mothers were tall in 60 per cent (three to eleven inches above the Engelbach and Schafer standard); obese (thirty pounds overweight) in 50 per cent; and showed advanced bone development (by twelve months) in 48 per cent.

TABLE 10

Deviations of height, weight and bone development of children of young diabetic parents

	Ht. + 3-7 in. Per cent	Wt. + 30 lb. Per cent	Bone age + 12 mo. Per cent
	Diabetic Mothers		
Sons	57	50	48
Daughters	31	20	48
	Diabetic fathers		
Sons	31	4	35
Daughters	31	2	35

Comparison of the rates of growth of the diabetic mother and her daughter are shown in figure 2. They are plotted on the same Wetzel grid. The mother developed diabetes in 1924 at the age of three years and became a typical diabetic dwarf. The daughter shows the trend toward gigantism.

In the interrelationship of the unusual growth pattern and occurrence of diabetes, islet hypertrophy and hyperplasia might be implicated. But the erythroblastotic who, to be sure, has not survived to comparable ages has not shown diabetes or growth peculiarities.

Influence of maternal diabetes on vascular pattern. The studies of the placenta of diabetic mothers by electron microscopy have shown microcapillary aneurysms and endarteritis not found in the nondiabetic. The newborn have shown coronary occlusion occasionally, more often thrombosis of the renal vein. Pulmonary hyaline membranes consisting of fibrin may be vascular in origin, resulting from increased capillary permeability.

Direct examination of the bulbar conjunctiva of the children of diabetic mothers showed venular dilatation in 75 per cent of those with abnormal glucose tolerance curves classified as diabetic or borderline.

Maternal parental morbidity represents a problem. Late maternal parental mortality is 10 per cent. There is no evidence of resentment on the part of the children, but they have questioned the relationship of their own birth to their mother's shortened life span.

The third generation exists. Currently it consists of ten healthy children under ten years of age.

DISCUSSION

Two major problems still confront us. These are the rapid progression of juvenile diabetes to a totally

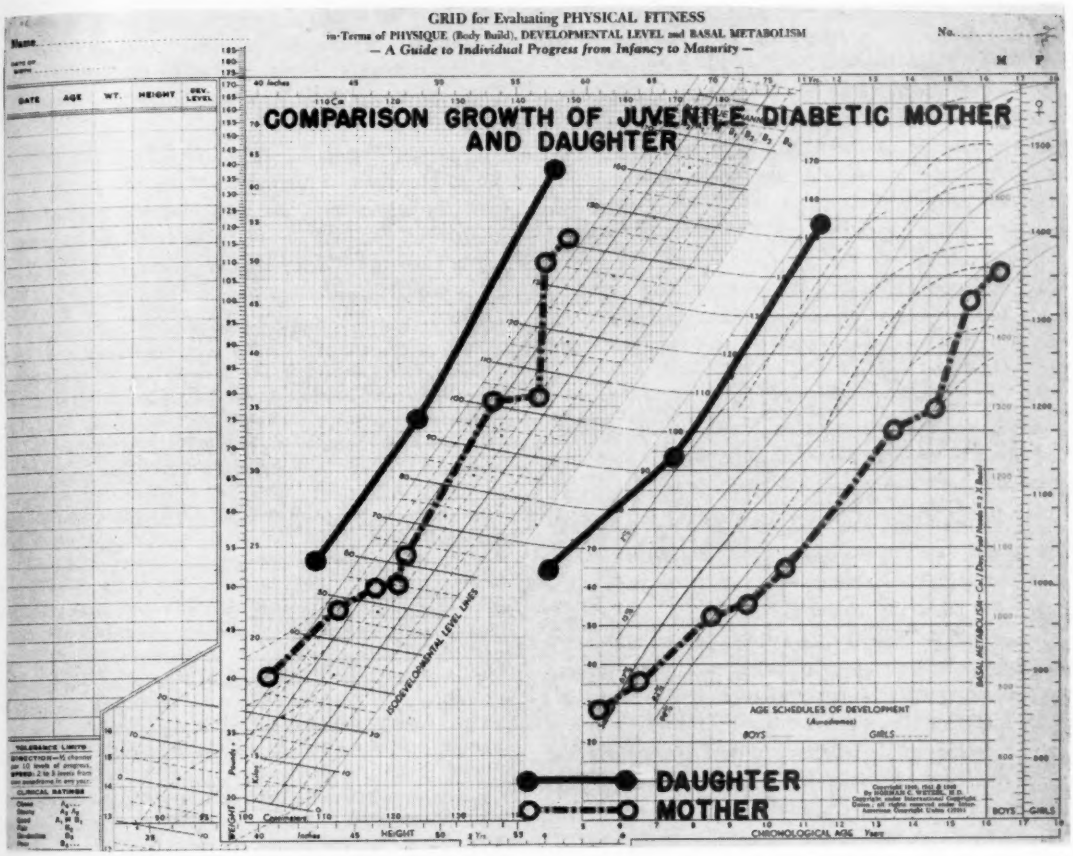
GRID for Evaluating PHYSICAL FITNESS
in Terms of PHYSIQUE (Body Build), DEVELOPMENTAL LEVEL and BASAL METABOLISM
— A Guide to Individual Progress from Infancy to Maturity —
COMPARISON GROWTH OF JUVENILE DIABETIC MOTHER AND DAUGHTER
DAUGHTER
MOTHER
AGE SCHEDULES OF DEVELOPMENT
BOYS
GIRLS
HEIGHT
CHRONOLOGICAL AGE

FIGURE 2

diabetic state and the acceleration of vascular lesions. Efforts to utilize substances found to be islet cell protecting in experimentally induced diabetes should be fostered. The remission phase is the ideal period for their use. Its frequency and duration are well established. The occasional response is encouraging.

Although early inception of vascular damage cannot be doubted, the reversible nature of some lesions has been recognized. Multiple causes undoubtedly influence the acceleration of diabetic angiopathy—a genetic trait. Two of the causes appear to be remedial, grossly poorly controlled diabetes and the results of infective processes.

With medical management, sodium restriction, chlorothiazide and other hypotensive agents, the progress of retinopathy and nephropathy may be retarded. Hypophysectomy must be re-evaluated in the light of reversibility of many lesions and improved results of total medical management. Less radical methods must be explored.

CONCLUSIONS

1. In the natural course of juvenile diabetes, after an acute onset, remissions occur but progression to total diabetes is evident in all save some 5 per cent.

2. The problems of growth and development have resolved themselves. Clinical and experimental observation suggest that growth hormone plays an etiological role.

3. Fertility is unimpaired but outcome of pregnancies in diabetic girls is affected by their disease. Pregnancy and/or its management may have a favorable effect upon diabetes and its vascular sequelae.

4. Early inception of vascular lesions is evident but the potential reversibility and/or remediability of some vascular lesions are recognized. Poor control of diabetes, and infections, influence the course of vascular damage but present forms of diabetes therapy achieve better control than was possible formerly, and new technics

reveal latent infections.

5. The incidence of crippling complications such as blindness is far less than is generally thought.

6. Successful control of two lethal factors, coma and sepsis, is shown conclusively. Duration of life in patients with nephropathy has been prolonged so that cardiovascular disease has replaced nephropathy as the chief cause of death.

7. Attempts to alter the course of juvenile diabetes are being made.

8. Childhood diabetics have entered their seventh decade and a few have equaled their expected life span.

9. A healthy second and a new third generation have been produced.

10. In less than twenty-five years the future of the childhood diabetic has changed from one of gradual extinction to one of prolonged survival to the third generation.

SUMMARIO IN INTERLINGUA

Diabete del Pueritia—Su Curso e Su Influentia in le Secunde e le Tertie Generation:
Conferentia Memorial Banting, 1960

1. In le curso natural de diabete juvenil, le declaration acute pote esser sequite per un remission, sed in loco de isto, progresso verso diabete total occurre in approximativemente 95 pro cento del casos.

2. Le problemas de crescentia e de disveloppamento se ha resolvite. Observationes clinic e experimental suggere que hormon de crescentia ha un rolo etiologic.

3. Le fertilitate non es afficite, sed le curso del pregnantia in femininas diabetic es influentiate per lor morbo. Pregnantia e/o su tractamento ha possibilemente un effecto benefic super diabete e su sequellas vascular.

4. Le inception precoce de lesiones vascular es evidente, sed le reversibilitate e/o le corrigibilitate potential de certe lesiones vascular es recognoscite. Le imperfecte regulation de diabete e le occurrentia de infectiones exerce un influentia super le curso del lesiones vascular, sed le currentemente disponibile modalitates therapeutic pro diabete resulta in meliorate grados de stabilisation in comparation con le passato, e nove technicas es capace a deteger infectiones in stato latente.

5. Le incidentia de complicationes invalidante, como per exemplo cecitate, es multo minus importante que lo que es generalmente supponite.

6. Successo es definitemente possibile in le manipulation de coma e sepse, que ambes es factores letal. Le duration del vita in patientes con nephropathia ha clarmente essite prolongate, de maniera que morbo cardiovascular ha reimplaciate nephropathia como causa principal de mortes in iste patientes.

7. Effortios a alterar le curso de diabete juvenil es in progresso.

8. Patientes con diabete juvenil ha supervivite usque al septime decennio de lor vitas. Plures ha attingite lor complete etate probabile.

9. Le procreation de un secunde e un tertie generation in bon stato de sanitate ha occurrite.

10. In minus que vinti-cinque annos, le prospectos del patiente con diabete juvenil ha cambiate frappantemente. Le certitude de extinction gradual es reimplaciate per le probabilitate de un supervivientia prolongate.

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The Metabolism of Adrenocortical Hormones in Pregnancy

It is widely recognized that many important alterations in metabolism occur in pregnancy which are determined by ovarian, pituitary, placental and adrenal cortical hormones. There is now unfolding a body of information indicating that the metabolism of hormones themselves often is decidedly different in the pregnant state. . . .

Measurement of the urinary excretion of corticosteroids has usually provided important information concerning corticosteroid metabolism. An increase in the excretion of glycogenic corticoids in the latter half of pregnancy was reported by E. Venning (*Endocrinology* 39:203, 1946). Subsequent measurements of free cortisol excretion in pregnancy is consistent with this finding. A number of other workers who measured the urinary excretion of corticosteroids with chemical methods, which included both the free and the conjugated metabolic products of cortisol, found that there was no significant increase in the excretion of total corticosteroids.

When methods became available for the measurement of unconjugated 17-hydroxycorticosteroids, mainly cortisol, in the blood, a significant rise to about twice the normal level was observed during the third trimester in pregnant women. An exaggerated rise in the plasma cortisol takes place after the administration of ACTH.

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Comparison of Plasma Insulin Levels Following Administration of Tolbutamide and Glucose

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The mechanism by which sulfonylureas induce hypoglycemia has been a subject of considerable debate. Since the literature in this field is already so vast that it can be touched upon only briefly here, the reader is referred to several excellent reviews.[1-3]

Whereas the bulk of evidence indicates that the hypoglycemic effect in mammals is dependent on the presence of functioning islet β cells and is therefore presumably a consequence of the stimulation of insulin secretion, it has not frequently been possible to demonstrate that the sulfonylureas produce the usual metabolic effects of injected insulin. Notably, studies with C^{14}-labeled glucose have generally revealed an unaltered rate of glucose utilization following administration of Na tolbutamide,[4-7] although slight increases were noted in one report.[5] In contrast, insulin administration in similar experiments usually produces a marked increase in C^{14}-glucose utilization.[4,8] However, one group of workers[7,10] has found that this effect may be absent if insulin is administered subcutaneously; hypoglycemia in the latter instance presumably results solely from the inhibition of hepatic release of glucose. Such a direct action of insulin on the liver has been disputed by Shoemaker et al.[11] but the objections of the latter group have been overcome by the recent experiments of Madison and co-workers.[12]

It has long been known that the liver is capable of concentrating and destroying insulin. The rapid accumulation of insulin-I^{131} by the liver has been demonstrated in vivo by external counting technics,[13] as well as by direct tissue analysis.[14] It has been shown that the liver removes approximately 50 per cent of insulin-I^{131} administered into the portal vein in a single transhepatic circulation[15] and the studies of Mirsky[16,17] and others[18,19] have demonstrated the marked insulin-degrading capacity of the liver in vitro. Furthermore, since the concentration of endogenous insulin would be higher in portal vein blood than in peripheral blood solely on the basis of dilution, endogenously secreted insulin would be expected to exert a relatively greater hepatic effect and lesser peripheral effect than the same dose of exogenous insulin administered into the peripheral circulation. Jacobs, Reichard, Goodman, Friedmann and Weinhouse[7] have suggested that, in contrast to the effect of exogenous insulin administered into a peripheral vein, the major action of endogenously secreted insulin may be to reduce the output of glucose from the liver rather than to increase glucose utilization by peripheral tissues and that this action could explain the hypoglycemic effect of tolbutamide in the absence of increased peripheral utilization of glucose.

In support of the hypothesis that the absence of definite peripheral effects of sulfonylureas is due to hepatic interception of endogenously secreted insulin are the observations of Pozza, Galansino and Foa,[20] in cross circulation experiments, that pancreatic vein blood but not mesenteric blood shunted into the peripheral circulation of other animals induces hypoglycemia in the recipient animals after tolbutamide administration to the donors.

Concentrations of insulin in the pancreatic vein assayed by the rat diaphragm technic[21] or by means of the hypoglycemic response of intact mice[22] were reported increased following tolbutamide administration but changes were considered of questionable significance when ADH mice were employed for plasma insulin assay.[23] It has also been reported recently that tolbutamide or metahexamide administration to human subjects is followed by marked increases in peripheral blood insulin as assayed with the rat epididymal fat pad.[24]

Since the bio-assays for insulin are of doubtful specificity and subject to the effects of certain ill-defined inhibitory substances reported to be present in plasma and since the difference in effect on peripheral glucose utilization produced by hyperglycemia and sulfonylureas has not yet been satisfactorily explained, it appeared

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of interest to compare changes in the plasma insulin concentration of peripheral blood following glucose and Na tolbutamide administration employing a sensitive and specific immuno-assay for human plasma insulin.[25-27]

METHODS

Methods employed in the immuno-assay of plasma insulin have been given in detail elsewhere.[26,27] Blood sugar concentrations were determined according to the method of Somogyi[28] or of Folin-Malmros.[29] Twelve fasting nondiabetic male subjects were given 1 gm. Na tolbutamide intravenously and this was followed forty minutes later by 2 mg. glucagon, 25 gm. glucose or 50 gm. glucose intravenously. In three experiments 2 ml. of normal saline was injected twenty minutes prior to the administration of the Na tolbutamide. Blood samples were taken immediately prior to the first injection and at twenty-minute intervals thereafter for a total of five to six specimens. Six nondiabetic subjects and four patients with early maturity-onset diabetes, never treated with insulin, were given 3 gm. Na tolbutamide by mouth after an overnight fast. A standard 100 gm. oral glucose tolerance test was performed under similar conditions within several days preceding or following the tolbutamide study. Blood samples were taken in the fasting state at one half, one and two hours following tolbutamide or glucose administration.

RESULTS

Blood sugar and plasma insulin concentrations of the four nondiabetic subjects who received intravenous injections of saline followed by Na tolbutamide (1 gm.) and glucagon (2 mg.) are shown in figure 1. Saline had no effect on the plasma insulin levels and tolbutamide produced a rise in all cases but the rise was generally less marked than that following glucagon.

In all patients who received 1 gm. Na tolbutamide intravenously, followed by 25 gm. or 50 gm. glucose intravenously, there was a distinct though temporary increase in insulin concentration following Na tolbutamide administration but this increase was less marked than that observed following glucose administration (figures 2 and 3).

In six nondiabetic and four early maturity-onset diabetic subjects, plasma insulin concentrations rose in every case following 3 gm. Na tolbutamide orally but a much greater increase in plasma insulin was observed following glucose by mouth in the same subjects (figgures 4A and 4B). The mean increase in plasma insulin concentration over the two-hour period was about two and one half to four times as great following glucose as following Na tolbutamide administration in diabetic and nondiabetic subjects (table 1). The blood sugar concentrations during both tests in both groups of subjects are shown in figure 5.

DISCUSSION

The consistent, albeit modest, increases in immunologically determined plasma insulin following tolbutamide

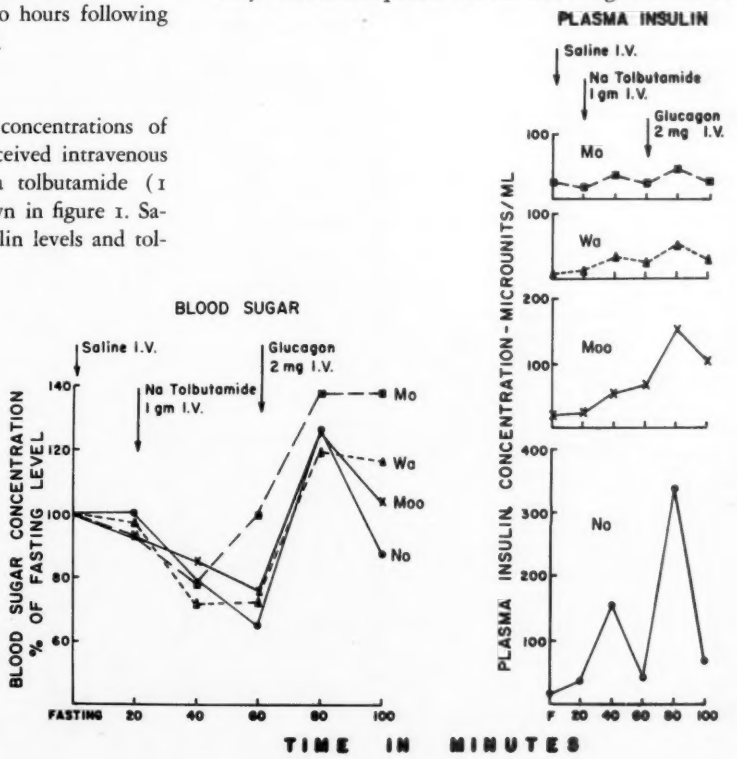

FIG. 1. Blood sugar and plasma insulin concentrations following intravenous administration of saline, 1 gm. Na tolbutamide and 2 mg. glucagon to nondiabetic subjects.

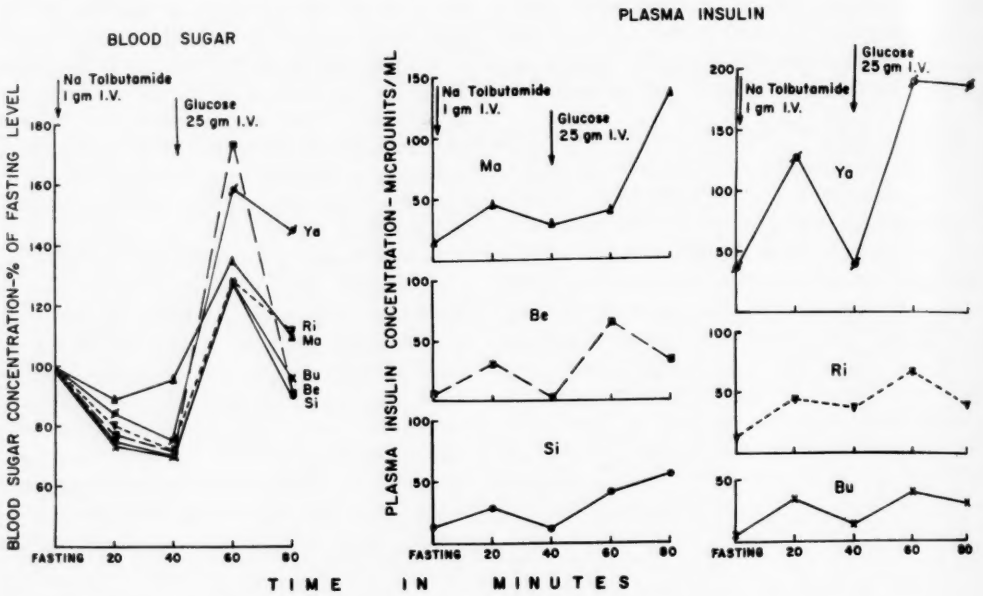

FIG. 2. Blood sugar and plasma insulin concentrations following intravenous administration of 1 gm. Na tolbutamide and 25 gm. glucose to nondiabetic subjects.

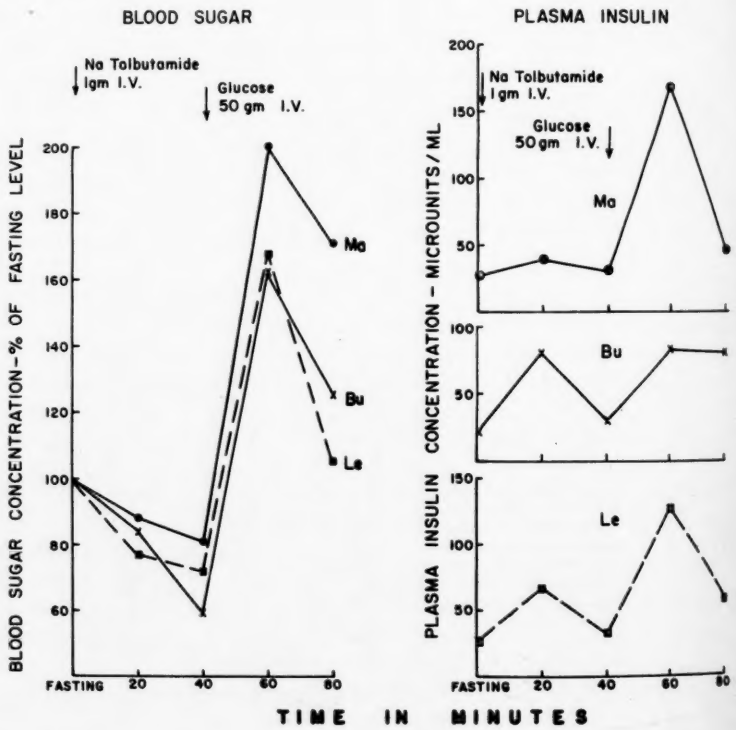

FIG. 3. Blood sugar and plasma insulin concentrations following intravenous administration of 1 gm. Na tolbutamide and 50 gm. glucose to nondiabetic subjects.

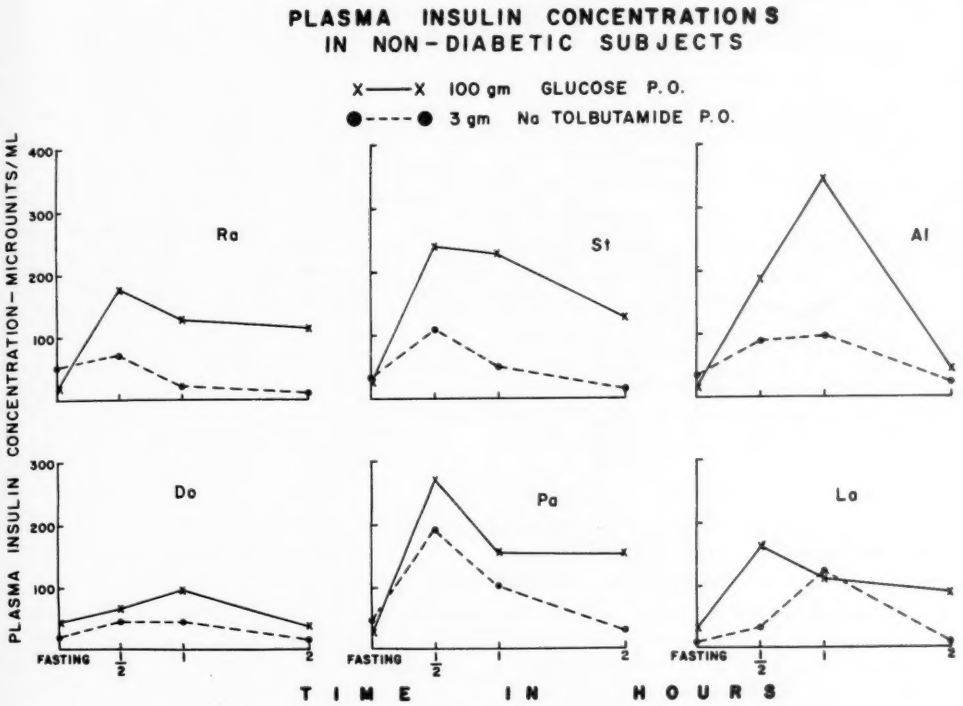

FIG. 4A. Plasma insulin concentrations following oral administration of 3 gm. Na tolbutamide and 100 gm. glucose to fasting nondiabetic subjects.

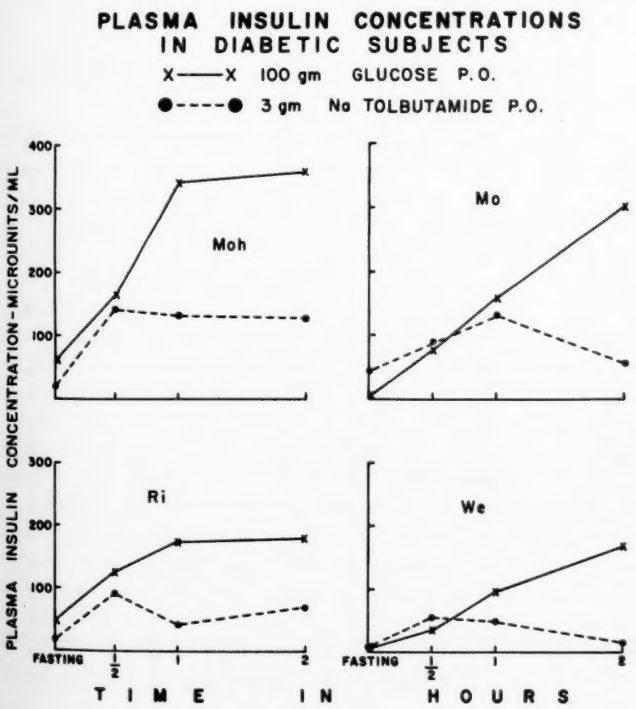

FIG. 4B. Plasma insulin concentrations following oral administration of 3 gm. Na tolbutamide and 100 gm. glucose to fasting diabetic subjects.

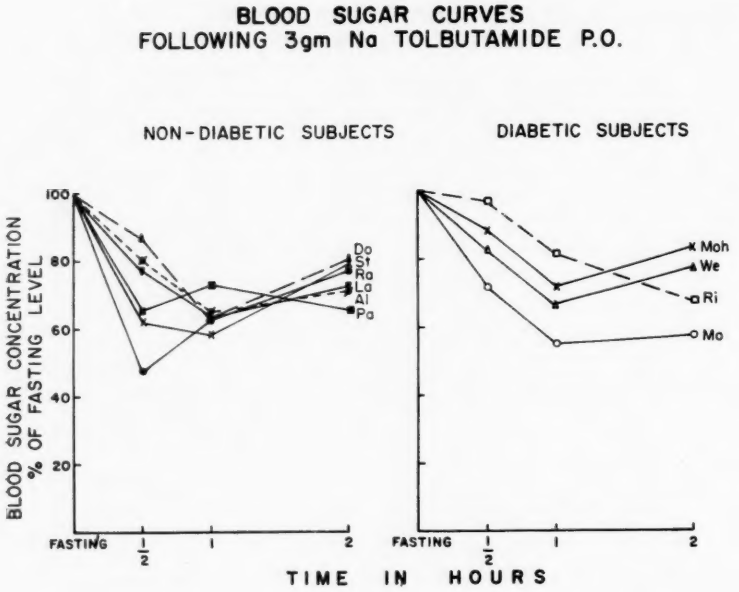

FIG. 5A. Blood sugar concentrations following oral administration of 3 gm. Na tolbutamide to fasting nondiabetic and diabetic subjects.

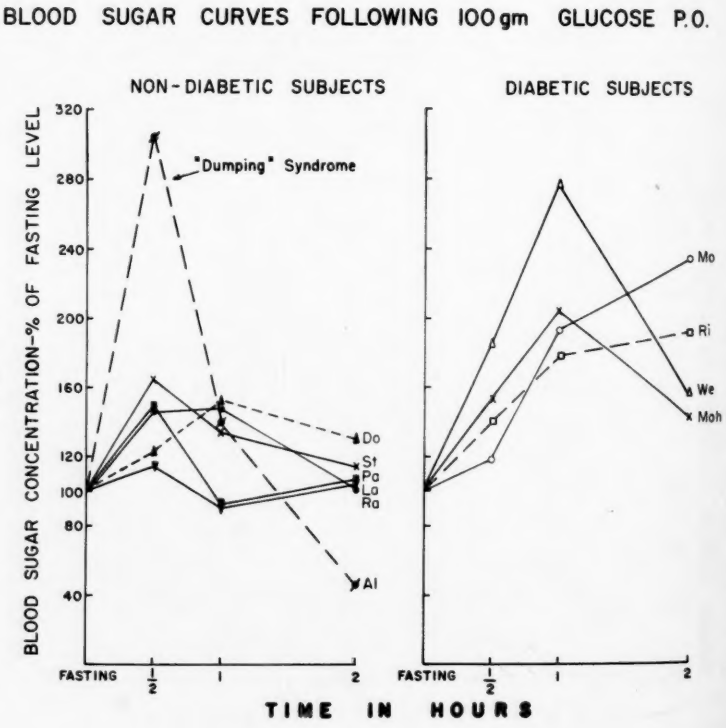

FIG. 5B. Blood sugar concentrations following administration of 100 gm. glucose to fasting nondiabetic and diabetic subjects.

TABLE 1

Mean increase in plasma insulin concentration above fasting level during two-hour period following oral administration of 3 gm. Na tolbutamide or 100 gm. glucose

Patient	Mean insulin concentration following	
	Na tolbutamide	Glucose
Nondiabetic subjects		
Ra	< 0 μU./ml.	100 μU./ml.
Do	19	50
Pa	50	142
St	18	165
Al	35	175
La	50	77
Average	28	119
Diabetic subjects		
Ri	40	100
We	30	81
Moh	92	200
Mo	45	147
Average	52	132

must be attributed to augmentation of insulin secretion, since the rise in insulin concentration appeared to be too rapid to be explained solely on the basis of inhibited degradation of insulin. Other studies have failed to establish significant effects of hypoglycemic doses of tolbutamide on the rate of insulin-I^{131} degradation in vivo.[30]

Although all patients studied showed increased plasma insulin concentrations following tolbutamide intravenously or orally, the responses usually were significantly less than following administration of glucose by the same route to the same patients. In general, the tolbutamide-induced rise in plasma insulin was of sufficiently moderate degree to be consistent with the absence of detectable effects on peripheral glucose utilization; in some cases the peak insulin concentration following tolbutamide was not higher than is occasionally observed in untreated fasting subjects.[26,27]

The responses in peripheral blood insulin concentration to glucose and tolbutamide administration serve to resolve the different effects of these agents on peripheral glucose utilization. The small increase in insulin secretion stimulated by tolbutamide, while adequate for an action on the liver, is evidently insufficient to produce a demonstrable acceleration of peripheral glucose utilization in the majority of cases, although such an effect might occasionally be exhibited.[8] These observations are consistent with the interpretation of Jacobs et al.,[7] Madison et al.,[29] Craig et al.[31] and others that inhibition of glucose release from the liver in the absence of any peripheral effect on glucose metabolism may result from a small endogenous secretion of insulin stimulated by tolbutamide. This mode of action is compatible with virtually all experimental data on the effects of tolbutamide. However, this interpretation does not necessarily imply that, *in general,* the physiologic effects of endogenously secreted insulin are manifested primarily on hepatic release of glucose. On the contrary, the significantly higher plasma insulin concentrations following glucose administration reported here are consistent with evidence derived from glucose-C^{14} experiments[32,33] that restoration of blood sugar to normal levels following glucose or feeding is effected primarily by increased peripheral utilization of glucose.

SUMMARY AND CONCLUSIONS

The concentration of insulin in peripheral blood, determined by immuno-assay, was increased in every instance following intravenous administration of 1 gm. sodium tolbutamide in twelve nondiabetic subjects and following oral administration of 3 gm. sodium tolbutamide in six nondiabetic and four early maturity-onset diabetic subjects. However, plasma insulin concentration was increased to a significantly greater extent following glucose administration by the same routes to the same subjects.

These findings are discussed in relation to previous work from which it is concluded that the present results are consistent with the hypotheses: (a) that inhibition of glucose release from the liver in the absence of accelerated peripheral utilization of glucose may result from tolbutamide stimulation of insulin secretion, and (b) that the stimulation of insulin secretion induced by glucose administration results in an increased peripheral utilization of glucose.

SUMMARIO IN INTERLINGUA

Comparation del Nivellos de Insulina in le Plasma post Administratationes de Tolbutamida e de Glucosa

Le concentration de insulina in le sanguine peripheric, determinate per immunoessayage, esseva augmentate sin exception post administrationes intravenose de 1 g de tolbutamida de natrium in dece-duo subjectos nondiabetic e post administrationes oral de 3 g de tolbutamida de natrium in sex subjectos nondiabetic e in quatro subjectos con diabete a declaration in juvene maturitate. Tamen, le concentration plasmatic de insulina esseva augmentate a grados significativemente plus marcate post administrationes de glucosa al mesme subjectos e per le mesme via.

Iste constatationes es discutite in relation a previe investigationes que justifica le assertion que le presente resultatos se trova in congruentia con le hypotheses (a)

que le inhibition del liberation de glucosa ab le hepate in le absentia de un accelerate utilisation peripheric de glucosa pote resultar ab le stimulation del secretion de insulina per le action de tolbutamida e (b) que le stimulation del secretion de insulina inducite per le administration de glucosa resulta in un augmento del utilisation peripheric de glucosa.

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The Mechanisms of Renal Glucosuria in Pregnancy

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Glucosuria, during the course of an otherwise uncomplicated pregnancy and in the absence of hyperglycemia, is a frequent occurrence. According to present concepts, the presence of glucose in urine is due to the inability of the renal tubule completely to reabsorb glucose from the glomerular filtrate, but until recently there have been no definitive studies to determine whether the glucosuria of pregnancy is due to an abnormally low tubular reabsorption, or to an increased filtration rate, or to the cumulative effect of both. The predominance of either of these mechanisms has also not been established. It is frequently stated that, in pregnancy, there is a lowering of the tubular reabsorptive capacity, yet this phenomenon has not been substantiated by appropriate clearance studies. Donato and Turchetti[1] have reported a series of patients with glucosuria in pregnancy in which some had a disproportionate rise in GFR over T_{mG}, and others had both a low T_{mG} and a low GFR. In this latter group, however, there was evidence of chronic renal disease.

In the present study the glomerular filtration rate and maximal tubular reabsorption of glucose of normal nonpregnant women, of pregnant women without glucosuria, and of pregnant women with glucosuria are compared in order to delineate more clearly the changes in glomerular-tubular relationships which occur during pregnancy and which may lead to glucosuria. Women with evidence of renal disease, impaired carbohydrate metabolism, or complications of pregnancy were excluded from this study.

MATERIALS AND METHODS

A. *Clinical Material*:

There were three groups of subjects: (a) normal nonpregnant women (controls); (b) pregnant women without glucosuria; (c) pregnant women with glucosuria.

(a) *Normal nonpregnant women*: The control subjects were fifteen active normal nonpregnant women. Their average age was thirty years (range twenty-four to thirty-eight); the average parity 2.3. Fourteen had not been pregnant within a year; one subject had had renal glucosuria during a previous pregnancy but was four months postpartum when studied as a control. One had a family history of diabetes in one grandparent, first detected at age eighty.

(b) *Pregnant women without glucosuria*: Sixteen normal pregnant subjects were studied during the seventh to thirty-sixth week of gestation (mean of twenty-five weeks). One subject had studies performed during two successive pregnancies. The mean age was 25.1 years (range twenty-one to thirty-two); the average parity was 1.1. Two had a family history of diabetes mellitus in a single grandparent.

(c) *Pregnant women with glucosuria*: Thirteen subjects with normal pregnancy and glucosuria were selected from a group of clinic and private patients. The mean age of this group was twenty-one years (range fourteen to twenty-eight) and the average parity was 1.6. Studies were performed during the thirteenth and thirty-ninth week of gestation, with a mean of thirty-three weeks. In all but two subjects, diabetes was excluded by a standard oral three-hour glucose tolerance test, in which 100 gm. of glucose were given. One other subject (M.H. of table 2) had a tolerance curve suggesting prediabetes as well as renal glucosuria.

B. *Procedure*:

Renal clearance of inulin was determined according to a technic previously described.[2] To ensure complete emptying of the bladder at the beginning and end of the three collection periods, the patients stood during the final irrigation with saline and air. The maximal tubular reabsorption of glucose (T_{mG}) was measured and calculated according to the technic of Goldring and Chasis[3] with minor modifications. A priming infusion containing 25 per cent glucose was followed with a constant infusion of 15.5 per cent glucose delivered by an infusion pump. In order to obtain arterialized blood for determination of plasma glucose, an indwelling needle was placed in the cephalic vein, and the arm was spirally wrapped with a three-inch wide strip of fiberglass containing heating wires. The current was adjusted with a rheostat so that the temperature over the skin was 41° C. Using this technic simultaneous arterial and arterialized venous blood samples yielded essentially the same concentrations of glucose, even within the normoglycemic range. Concentrations of glucose ranged between 368 and 1,180 mg. per 100 ml. of plasma,

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generally rising slowly during the procedure. In relating plasma concentrations to collections of urine, a delay time of eight minutes was assumed. In all instances the ratio of filtered to reabsorbed glucose was higher than the critical value of 1.5 necessary to ensure total saturation of the tubular reabsorptive mechanism. When the patients were first catheterized, urine samples were taken for microscopic examination, Gram stain, and culture, as well as for qualitative testing for glucose and protein.

C. *Analytical Methods*:

Glucose was determined by the iodometric technic of Somogyi[4] after precipitation of proteins with zinc sulfate and sodium hydroxide.[4] Inulin was estimated by Schreiner's modification[5] of the resorcinol method of Roe. Glucose interferes with the determination, but, as shown in figure 1, this interference is linear at all concentrations of glucose encountered. One milligram of glucose gave a color equivalent to 0.014 mg. of inulin, and analyses for inulin were corrected accordingly. A similar linearity is seen in the data of Froesch, Reardon and Renold,[6] using the Higashi and Peters modification of the resorcinol method, but the degree of interference is only approximately half that found by us. Using our correction factor, recoveries of added inulin in the presence of glucose in the range of concentrations encountered in the study were satisfactory. When corrected in this way, essentially the same values for inulin were obtained as when glucose was removed either by yeast, or by glucose oxidase according to the technic of Froesch, et al.[6]

D. *Statistical Analyses*:

Methods of statistical analysis were as previously reported.[2]

E. *Glucose Tolerance Tests*:

Criteria for abnormality of glucose tolerance tests were those used by Wilkerson, et al.[7]

F. *Urinary Glucose*:

Glucose oxidase testing methods were used to detect urinary glucose.

RESULTS

A. *Normal nonpregnant women (controls)*:

The mean glomerular filtration rate (during infusion of hypertonic glucose) in fifteen normal nonpregnant women was 124 ml./min. (S.E. 4.5). The mean tubular maximum reabsorption for glucose was 366 mg./min. (S.E. 15.8), which is higher than the mean for normal females reported by Smith, et al.[8] The mean GFR/T_{mG} ratio was 0.338 for this group; Smith[8] reported a ratio of 0.395 for eleven normal women.

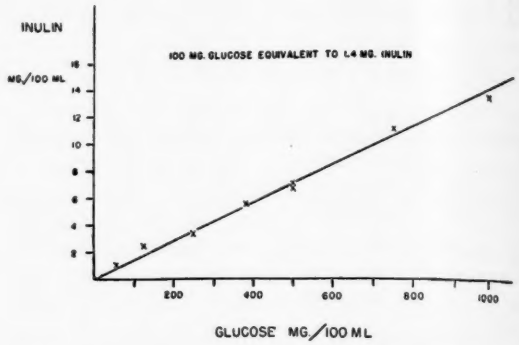

FIG. 1. The interference caused by added glucose in the resorcinol method for the determination of inulin. On the abscissa is shown the quantity of glucose added in recovery experiments and on the ordinate its equivalent in terms of inulin.

B. *Pregnant women without glucosuria*:

In table 1 the individual values for body surface area, glomerular filtration rate as measured by inulin clearance, tubular maximum reabsorptive rate (T_{mG}), and the ratio of filtered to reabsorbed glucose are given for each of the normal pregnant women. None had shown glucosuria on repetitive examination. The average glomerular filtration rate in this group was 151 (S.E. 4.5). The glomerular filtration rates are similar to those reported by Sims and Krantz.[2] The mean T_{mG} was 378 (S.E. 19.9), which is not significantly different from the average control T_{mG}'s. Studies during the seventh and during the thirtieth week of pregnancy of one subject (M.McA.) yielded essentially the same results. In subject J. C. separate studies were made in successive pregnancies. It will be noted that the GFR and T_{mG} in the eleventh week of the second pregnancy were much higher than during the thirty-fourth week of the first.

C. *Pregnant women with glucosuria*:

Table 2 lists the results of studies on those pregnant women who repeatedly showed glucosuria. All but two of these patients had oral glucose tolerance tests, as indicated. With the possible exception of M. H., who might be considered "prediabetic" by the criteria of Wilkerson,[7] tolerance curves were within the normal range but glucosuria occurred during the tests. The two subjects who did not have tolerance tests (M. L. and M. C.) showed glucosuria repeatedly on random urine testing, and both had normal fasting blood sugars. Each excreted 1.6 gm. of glucose in twenty-four hours. The mean GFR was 151 (S.E. 7.5) which is similar to the GFR of the normal pregnant group. The average T_{mG} was 310 (S.E. 18). This is significantly lower than the T_{mG}

TABLE 1

Normal pregnant women

Subject Age Parity	Duration of pregnancy (weeks)	Body surface area sq./m.	Clearance of inulin ml./min. 1.73 sq. m.	Tm_G mg./min./ 1.73 sq. m.	Ratio: Filtered to reabsorbed glucose
G.B. 21 0	35	1.65	165	399	2.8
C.B. 23 1	17	1.79	146	345	2.9
O.B. 30 3	28	1.80	143	400	2.4
S.C. 21 0	36	1.83	121	302	2.2
J.C.(I)* 24 0	34	1.72	157	306	2.5
J.C.(II) 25 1	11	1.72	172	522	2.6
J.Co. 26 1	35	1.69	188	434	2.7
E.D. 25 0	32	1.80	149	416	2.4
J.D. 23 0	16	1.72	151	526	1.9
M.McA. 32 3	7 30	1.47 1.58	131 131	316 303	2.0† 2.5
A.M. 24 0	24	1.65	126	217	4.1
J.M. 28 2	14	1.72	170	351	2.3
C.M. 23 0	34	1.63	143	453	2.8
A.Mi. 23 0	28	1.53	163	298	4.1
E.P. 30 3	24	1.62	173	423	2.5
E.S. 26 1	17	1.72	142	325	2.6
M.W. 24 1	3	1.52	146	424	3.0
Mean±S.D.			151.4±19	378±82	
Standard error of the mean			4.5	19.9	
Mean±S.D. for fifteen controls			124±17	366±61	
Standard error of the mean			4.5	15.8	

*Values in two separate pregnancies.
†Not used in statistical calculation, same pregnancy; second value used in calculation.

of either the controls ($p < 0.05$) or the normal pregnant women ($p < 0.01$).

D. *Comparison of measurements of renal function*:

Filtration rates. In pregnancy, glomerular filtration rates were consistently high, in the range of 150 ml./min., and differed little whether or not the subject was normoglycemic, hyperglycemic, or hyperglycemic and glucosuric, as illustrated in figure 2. The GFR values obtained for the nonpregnant women in this series are higher than those of normal female subjects tested previously in this laboratory;[2] the increase probably reflects the hypervolemia induced by the infusion of large amounts of hypertonic glucose.

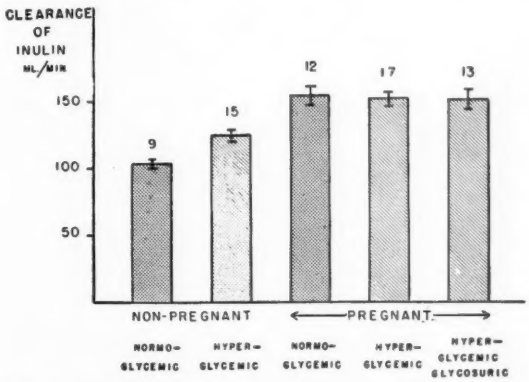

FIG. 2. Variations in the glomerular filtration rates measured by inulin in normal female controls (column 1), normal subjects undergoing measurement of glucose Tm (column 2), in normal pregnant subjects (column 3), pregnant subjects undergoing measurement of glucose Tm without previous glucosuria (column 4), and with established glucosuria (column 5). The number of subjects in each group is given above the bars, and the vertical lines represent the standard error of the means. Data for columns 1 and 3 taken from Sims and Krantz.[2]

The relationship of Tm_G *to* GFR. The regression of Tm_G on GFR of each group is illustrated in figure 3 with both measurements corrected for surface area. The proportionate increase of Tm_G and GFR reflects an individual variation in functional renal mass other than that related to differences in surface area. A similar relationship was noted by Smith, et al.[6]

The regression lines for the nonpregnant, pregnant, and pregnant-glucosuric groups have about the same slope but are displaced one from the other. The mean ratio of GFR/Tm_G was 0.338 in the nonpregnant group, 0.401 in the normal pregnant group and 0.486 in the glucosuric-pregnant group, suggesting that even in the normal pregnant women there is a relative preponderance of filtered load.

If lines of regression are calculated using data un-

TABLE 2

Glucosuric pregnant women

Subject Age Parity	Duration pregnancy (weeks)	Body surface area (sq. m.)	Glucose tolerance Blood glucose (mg./100 ml.) Urine glucose (gm. per cent) 0 hr.	½ hr.	1 hr.	2 hr.	3 hr.	Clearance of inulin ml./min. 1.73 sq. m.	Tm_G (mg./min./ 1.73 sq. m.)	Ratio: Filtered to re-absorbed glucose
M.M. 21 0	38	1.83	88 ½%	152 ¾%	141 2%	128 1%	106 1%	157	386	1.9
L.Mc. 23 0	26 Postpart. 14	1.45 1.37	88	154	132	93	58	156 131	302 346	4.5 3.5
D.J. 21 1	13	1.52	87 0%	112 ½%	105 1%	93 1%	102 ¾%	208	416	3.7
M.H. 22 4	39	1.70	77 0%	158 ¾%	200 2%	185 1%	97 2%	170	304	3.0
P.Be. 20 0	37	1.76	79	137	130	113	120	162	294	2.8
N.P. 17 0	34	1.64	73 0%	109 ¼%	104 1%	134 ½%	117 ½%	140	231	4.8
M.Mo. 25 5	39	1.70	88 ½%	152 ¾%	141 2%	128 1%	106 1%	167	421	2.9
E.L. 14 0	31 Postpart. 1	1.60 1.60	86 0%	124 ½%	163 2%	123 1%	106 ¾%	132 128	264 326	3.1
M.L. 28 3	39 Postpart. 14	1.75 1.63	84	126	115	113	99	130 99	258 266	3.0 3.0
G.L. 18 0	30	1.52	86					127	289	3.1
B.H. 23 1	38	1.86	81 0%	152 0%	144 ¾%	138 ½%	103 ½%	123	264	3.3
P.Bu. 22 1	33	1.64	103 0%	134 —	115 1%	96 1%	113 1%	105	238	3.4
M.C. 29 4	35	1.43	69					176	358	2.4
Mean±S.D. Standard error of the mean								151±27 7.5	310±65 18	
Mean±S.D. for fifteen control subjects Standard error of the mean								124±17 4.5	366±61 15.8	

corrected for surface area, the deviations of individual values from the lines are essentially the same as for corrected data.

E. *Postpartum studies*:

In three of the women who showed glucosuria during pregnancy (M. LaR., L. McG., and E. L.) repeat studies were performed 14, 14, and 1 week postpartum respectively. In each instance the GFR decreased: 130 to 99; 156 to 131; and 138 to 128 ml./min., respectively. On the other hand, the Tm_G values increased slightly: 258 to 266; 302 to 346; and 264 to 326 mg./min., respectively. Although the changes in all three patients

were in the same direction, the variations are within one standard deviation and cannot be considered significant.

F. *Miscellaneous observations*:

All patients in the control, normal pregnant, and pregnant-glucosuric groups had a decreased hematocrit at the end of the procedure. Venous pressure determinations were made in most subjects and showed no elevations above normal range. Several women experienced painful leg cramps during the latter part of the procedure. Serum electrolytes did not show abnormal values. Many of the women had symptoms of hypoglycemia at one to two hours following the procedure.

DISCUSSION

Is the normoglycemic glucosuria of pregnancy the result of an abnormally low tubular reabsorption of glucose or an abnormally high filtered load of glucose, or a combination of both factors? Sims and Krantz[2] and others have demonstrated that during pregnancy the GFR increases from a normal mean of 103 ml./min. to 150 ml./min. The results of the present study are confirmatory; the mean GFR of our normal pregnant group was 151 ± 4.5 ml./min. and of the pregnant glucosuric groups was 151 ± 7.5 ml./min. Although the mean of both groups is significantly elevated above that of the nonpregnant controls, neither the mean nor the variation about the mean of the two groups differs significantly. Thus the glucosuric pregnant women are not distinguished from the nonglucosuric pregnant women by an abnormally high GFR.

On the other hand, the mean Tm_G of glucosuric pregnant women (310 ± 18 mg./min.) is strikingly and significantly ($p < 0.01$) lower than the mean Tm_G of nonglucosuric pregnant women (378 ± 20 mg./min.). This latter value does not differ significantly from that mean of nonpregnant women (366 ± 16 mg./min.).

The results suggest that glucosuria occurs when the normally increased GFR of pregnancy is associated with an abnormally low Tm_G. The increased GFR of pregnancy, without a correspondingly increased Tm_G, is represented by the displacement to the right without significant change in slope of the regression line of the normal pregnant group (figure 3). The further displacement of the regression line of the glucosuric pregnant women reflects the lower Tm_G of this group, when related to GFR. It is essential to recognize that there is a normal variation of Tm_G with GFR, as the slope of the regression lines of Tm_G on GFR is the same in all groups as shown in figure 3. Otherwise the Tm_G of some glucosuric women would appear deceptively normal, unless it is considered in relation to the GFR.

The present data indicate that pregnancy increases the filtered load of glucose without an appreciable increase of the tubular capacity to reabsorb glucose, thus making all pregnant women more liable to exhibit glucosuria. Detailed serial studies antepartum and adequate post-

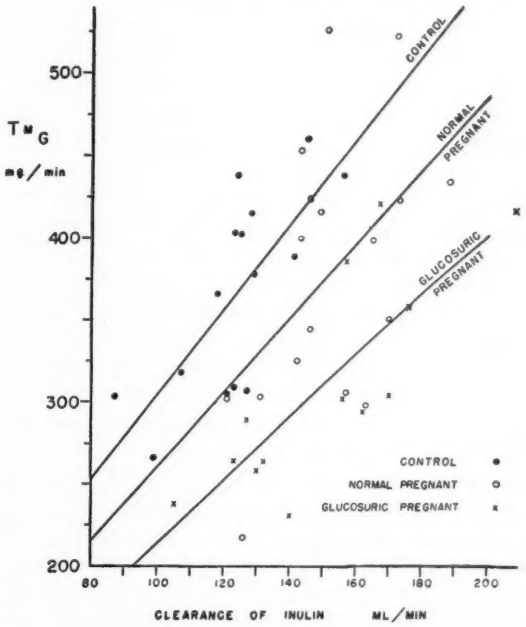

FIG. 3. Regression lines of Tm_G on GFR for control, normal pregnant and glucosuric women. All values are corrected to standard surface area (1.73 sq. m.). See text for discussion.

partum studies are necessary to determine whether the Tm_G is actually *lowered* during pregnancy in any of the glucosuric subjects. Allowance would have to be made for the fact that renal function may remain altered for some months after delivery.[2] Unfortunately, it was only possible to obtain postpartum studies on three subjects in the present series; the results were not conclusive.

Reubi[9] has made titration studies in renal glucosuria in which the filtered load of glucose has been progressively increased, and has found that the condition may be associated with both heterogeneous and homogeneous populations of nephrons. Definitive evidence is not yet available as to whether in pregnancy the relatively mild glucosuria is produced by relatively few nephrons or uniformly by the group. However, the fact that there is a considerable area of overlap between glucosuric and nonglucosuric subjects, with respect to the over-

all relationship of Tm_G to GFR, may be considered evidence for lack of a homogeneous population of nephrons. On the other hand it must be realized that the measurement of filtration rate, especially in pregnancy, is subject to many variables, hemodynamic and mechanical, and the values obtained do not necessarily reflect those prevailing at the time the subject exhibited glucosuria.

In their study of patients with glucosuria in pregnancy, Donato and Turchetti[3] noted that their patients fell into two groups. The first group had low filtration rates and low Tm_G values. On the basis of the presence of proteinuria, hematuria, edema, premature delivery, and placental infarcts the authors considered that these subjects were suffering from a form of chronic renal impairment. In the second group the filtration rates were elevated, and it was felt that glucosuria resulted from the disproportionate increase in filtered load.

Ackerman, Fajans and Conn[10] have advanced evidence that renal glucosuria may be a forerunner of diabetes mellitus in a significant number of cases. To date there is no conclusive evidence that glucosuria in pregnancy bears such a relation to diabetes. In this small series we found no evidence to suggest prediabetes, such as excessive-sized infant, family history of diabetes, prematurity, abortion, or stillbirth among glucosuric subjects, and with one exception glucose tolerance tests were normal. This is in contrast to the findings of Miller, et al.,[11] who noted in eleven glucosuric patients selected from a group of 137 pregnant subjects a high incidence of these complications.

Factors which may contribute to the increase in filtration rate in pregnancy and hence in the filtered load of glucose have been reviewed in a previous communication.[2] The physiological increase in blood volume and decrease in colloid osmotic pressure observed during pregnancy may result in an increased glomerular filtration rate, although renal plasma flow declines normally in pregnancy prior to the peak in plasma volume. This increase in renal function in pregnancy may be mediated by endocrine factors. Of these, i.e., thyroid hormone, growth hormone, estrogens, and adrenal cortical steroids, only the 11-oxy adrenocortical steroids have been suspected of decreasing the renal tubular reabsorption of glucose, although evidence is conflicting on this point. Kendrick, et al.[12] found that only certain individuals responded to cortisone or ACTH with a fall in Tm_G. Dustan, et al.[13] found that ACTH lowered Tm_G in a majority of their subjects and Kass, et al.[14] found similar changes. Each of these noted some increase in filtration rate following ACTH, and findings in regard to blood glutathione were variable. Conn[15] reported that ACTH induced glucosuria in man and also that Cushing's disease was briefly reversed by administering glutathione, while Lazarow[16] found the opposite in rats. Froesch, et al.[17] has recently shown in short-term studies with prednisone in four normal males, and two patients with glucosuria, that filtration rate was increased but Tm_G was unaltered. Thus it remains to be proved that, while 11-oxy adrenocortical steroids may increase the filtration rate and filtered load of glucose, they also reduce the capacity of the tubules to reabsorb glucose.

A consequence of the increased filtration rate in pregnancy, which may produce glucosuria in normal subjects, is the effect upon pregnant diabetics. Since glucosuria may develop at lower concentrations of blood glucose, these patients may be unusually susceptible to hypoglycemic reactions secondary to excessive insulin. This may explain the difficulty in regulation and tendency toward reactive ketosis of many of these diabetic patients during pregnancy. Perkoff[18] has made a similar observation. A recent study in this laboratory has shown that a similar relationship may be seen in a diabetic patient with impaired renal function due to intercapillary glomerulosclerosis.[19]

SUMMARY

1. Comparative studies of glomerular filtration rate and maximum tubular reabsorption of glucose have been carried out on fifteen nonpregnant normal women, sixteen pregnant women without glucosuria, and thirteen pregnant women with glucosuria unaccompanied by hyperglycemia.

2. The mean glomerular filtration rate of both groups of pregnant women, with or without glucosuria, was the same and was significantly elevated compared to the nonpregnant controls.

3. The mean tubular maximum reabsorption of glucose (Tm_G) was significantly lower in pregnant women with glucosuria than in those pregnant women without glucosuria or in the control subjects. Evidence is not yet available whether Tm_G is actually *lowered* during pregnancy.

4. The relationship of Tm_G to GFR, as illustrated by the slope of regression lines, is not significantly different whether the subject is nonpregnant, or pregnant, or pregnant with glucosuria. However, the ratio of GFR/Tm_G is greater in the pregnant group compared to the nonpregnant group, and greatest in the pregnant women with glucosuria. Glucosuria is thus facilitated by the preponderance of filtered load over tubular reabsorptive capacity.

5. The potential effects of superimposed renal glucosuria in pregnant diabetic women on the control of diabetes, incidence of hypoglycemia, and reactive ketosis are discussed.

6. The possible effects of hormonal factors in inducing glucosuria in pregnancy are discussed.

SUMMARIO IN INTERLINGUA

Le Mechanismos de Glucosuria Renal in Pregnantia

1. Studios comparative del rata de filtration glomerular e del maximo de reabsorption tubular de glucosa esseva executate in dece-cinque non-gravidas normal, dece-sex gravidas sin glucosuria, e dece-tres gravidas con glucosuria non accompaniate de hyperglycemia.

2. Le rata medie de filtration glomerular in le duo gruppos de gravidas—le glucosuriales e le non-glucosuriales—esseva le mesme e esseva significativemente elevate in comparation con le non-pregnante controlos.

3. Le valor medie del maximo de reabsorption tubular de glucosa (Tm_G) esseva significativemente plus basse in gravidas con glucosuria que in gravidas sin glucosuria o que in non-gravide subjectos de controlo. Le constatationes facite usque nunc permitte non ancora asserer si o non Tm_G descende durante le pregnantia.

4. Le relation de Tm_G al rata de filtration glomerular (RFG), reflectite in le coefficiente de direction del lineas de regression, non differe significativemente secundo que le subjecto es non gravide, o gravide, o gravide e glucosurial. Tamen, le proportion de RFG/Tm_G es plus grande in le gruppo pregnante que in le gruppo non pregnante. Illo es le plus grande in le gruppo del feminas pregnante con glucosuria. Il seque que glucosuria es favorate per un preponderantia de carga filtrate super le capacitate reabsorptive del tubulos.

5. Es discutite le effectos potential, in feminas pregnante, de glucosuria renal super le stabilisation de diabete, le incidentia de hypoglycemia, e le reactive cetosis.

6. Es discutite le effectos possibile de factores hormonal in le induction de glucosuria in gravidas.

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Predictive Failure of Erythrocyte Glucose-6-phosphate Dehydrogenase Activity in Sulfonylurea Hepatotoxicity

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Clinical trials of oral hypoglycemic sulfonylurea drugs have disclosed occasional hepatotoxicity from chlorpropamide, carbutamide, and metahexamide; chiefly because of the seriousness of these complications, the latter two drugs are not marketed in this country. The nature of these biochemical disturbances remains a mystery, since the changes can not be produced easily in animals.

Recently Hamwi reported the simultaneous development of mild hemolytic anemia and a toxic hepatitis in a forty-six-year-old Negro woman who had received metahexamide, 250 mg. daily, for fifteen days.[1] Her erythrocytes were found to be deficient in glucose-6-phosphate dehydrogenase—the same enzymatic defect responsible for the hemolytic anemias due to primaquine,[2] naphthalene,[3] fava beans, etc.[4] This finding suggested that the hepatotoxicity might be on the basis of the same or a related enzymatic defect. Or, to restate the problem, perhaps the hepatotoxicity occurs only in patients enzymatically predisposed to it. If this were true, a screening test would easily separate the many diabetics who could take the drugs with hepatic impunity from the few who could not. To test this hypothesis, it seemed logical to screen for G6PD (glucose-6-phosphate dehydrogenase) deficiency in the erythrocytes.

METHODS AND MATERIALS

The screening method was obtained through the kindness of Drs. Arno Motulsky and Jean Kraut of the University of Washington.[5]

A hemolysate of 0.04 ml. blood in 1.5 ml. distilled water is placed in a small test tube to which is added the following:* in second column.

0.4 ml. TRIS buffer (8.95 gm. in 100 ml. distilled water, 0.74 M, *p*H 8.5).

0.5 ml. Brilliant Cresyl Blue Dye (40 mg. in 125 ml. distilled water, 10^{-3} M).

0.4 ml. distilled water.

0.1 ml. TPN (0.1 mg.).

0.1 ml. glucose-6-phosphate (165 mg. in 10 ml., 5×10^{-2} M).

Each tube is mixed well, covered with a layer of mineral oil, and incubated at 37° C. in a water bath. Beginning at seventy-five minutes of incubation, the tubes are carefully inspected in natural light for a color change. This change occurs in the following sequence: blue-green to gray-green to light green with streaks of pink to pink with streaks of green to pink. The first appearance of pink is taken as the end point. Normal cells can accomplish decolorization of the dye within 100 minutes by this method. After some preliminary experience had been gained 140 male veterans were tested shortly after admission to the hospital. Tests were done on fresh blood in batches of ten to twenty at a time and results were checked by two observers.

RESULTS

The composition of the patient population and the results obtained are shown in table 1. It is obvious that 138 patients displayed normal erythrocyte G6PD activity while two patients were definitely abnormal. Both these patients were admitted because of gastrointestinal bleeding and one was moderately anemic at the time of testing, but the hematocrit was not low enough to explain the G6PD depression. Neither patient had any history of primaquine or other drug sensitivity. Extensive hematologic studies were not carried out in these men.

Of the thirty diabetic patients, twelve (five white and

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*TRIS buffer (tris hydroxymethylaminomethane), TPN (triphosphopyridine nucleotide), and glucose-6-phosphate as the disodium salt were obtained from the Sigma Chemical Co. Brilliant Cresyl Blue was obtained as the powder from National Aniline Division, Allied Chemical and Drug Co.

TABLE 1

Results of G6PD screening test

Patients	Number	Reduction after minutes 75	90	100	110	125	140
I. Diabetic (30)							
a. white	15	14	1	—	—	—	—
b. Negro	14	13	1	—	—	—	—
c. oriental	1	1	—	—	—	—	—
II. Nondiabetic (110)							
a. white	42	39	1	—	—	—	1
b. Negro	68	67	1	—	—	—	1
Total	140	134	4	—	—	—	2

seven Negro) received oral hypoglycemic agents. One of the five white patients had developed alkaline phosphatase elevation while receiving metahexamide eight months before the screening for G6PD activity, and one of the seven Negro patients demonstrated a similar elevation while receiving chlorpropamide at the time of screening. Details of these hepatotoxic manifestations are noted in table 2. Both patients manifested perfectly normal G6PD activity.

DISCUSSION

The study was instituted to test the hypothesis that hepatotoxicity from the oral sulfonylurea drugs was limited to those patients with G6PD deficiency on screening test. It is obvious that this hypothesis must be rejected in view of the two patients whose hepatotoxicity is characterized in table 2.

The assumptions underlying this study require brief comment. The first is that this screening method actually does reveal genetic G6PD deficiency of the erythrocytes; Motulsky has made precise quantitative assays that indicate this is true and the point was not reinvestigated in the present study.

The second assumption is that alkaline phosphatase elevation, with or without symptoms, is always a precursor of progressive hepatotoxicity which may have serious consequences if the drug is continued indefinitely. This is a debatable point. Some observers have found the alkaline phosphatase to rise during therapy and then to return to normal levels even though the drug is continued.[6]

Granted that such patients pose no problems clinically, the extent and significance of the hepatocellular damage cannot be dismissed lightly, in view of recent histological studies.[7,8] Nowadays the conservative clinician usually considers a rising alkaline phosphatase a valid indication for stopping the medication, whether the patient is symptomatic or not.

The third assumption is that G6PD activity in the red cell parallels its activity in the liver. This point is unsettled because of scanty data on the subject. Quantitative analysis of hepatic G6PD activity in cases with proved erythrocyte deficiency has been reported in only three cases; hepatic activities were 0.03, 0.04, and 0.05 unit compared to the normal range of 0.05 to 0.13 unit.[9] These results are suggestive of a mild hepatic

TABLE 2

Clinical data in two cases of sulfonylurea hepatotoxicity

Patient	I	II
Age and race	40, white	44, Negro
Duration of diabetes	8 years	7 years
Maximum insulin dosage	70 units	40 units
Drug and dosage received at time of first hepatotoxicity	Metahexamide, 5.3 gm. over twenty-three-day period	Chlorpropamide, 32.5 gm. over fifty-day period
Symptoms	Headache, anorexia	None
Alkaline phosphatase elevation	18 B.U. (to 9.4 in one month)	13.7 B.U. (to 6.2 in one month)
Serum bilirubin	0.50 mg. per cent	0.40 mg. per cent
Bromsulphalein retention	5.4 per cent in 45 minutes	5 per cent in 45 minutes
Cephalin flocculation	—	Negative
Thymol turbidity	0.5 units	0.4 units
Prothrombin time	90 per cent	100 per cent
Liver biopsy	Normal (two weeks after stopping metahexamide)	Pigmented granules (probably bile) in liver cells
G6PD activity on screening	Normal	Normal

deficiency, contrasting with a severe erythrocyte deficiency in the same patients.

The final and basic assumption is that hepatic G6PD is involved somehow in the hepatotoxicity produced by the sulfonylurea drugs. This is still entirely speculative. In fact, the concept that there is any permanent enzymatic defect in the livers of these patients is completely unsupported by fact. However, very little work has been done on the biochemistry of hepatotoxic reactions.

The predictive failure of the screening test in this study indicates only that one or more of these assumptions is faulty, but casts no light on the biochemical sequence of events of sulfonylurea hepatotoxicity. When this is known, a practical and accurate screening test may become available that will tell the clinician which diabetics will develop hepatotoxicity on sulfonylurea therapy. Clearly, the present test for erythrocyte G6PD activity is not the answer.

SUMMARY

The suggestion that erythrocyte glucose-6-phosphate dehydrogenase deficiency might be associated with a tendency to hepatotoxicity during oral hypoglycemic sulfonylurea therapy was put to the test by applying a simple screening test to 140 hospitalized patients, thirty of whom were diabetic. Twelve of the thirty received sulfonylurea drugs and two of these developed mild hepatotoxicity despite normal enzyme activity as measured by the screening test.

SUMMARIO IN INTERLINGUA

Deficientia del Activitate de Dishydrogenase Glucosa-6-Phosphatic del Erythrocytos in Hepatotoxicitate Sulfonylureal

Le notion que deficientia del dishydrogenase glucosa-6-phosphatic in le erythrocytos es associate con un tendentia de disveloppar hepatotoxicitate in le curso de therapia hypoglycemic oral a sulfonylurea esseva probate per le application de un simple test a 140 hospitalisate patientes, incluse trenta con diabete. Dece-duo del trenta recipeva drogas sulfonylureal, e duo de istes disveloppava leve grados de hepatotoxicitate in despecto de normal activitate enzymatic secundo le test usate.

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Nutrition and Chronic Disease Control

American children are considerably taller and heavier than they were twenty or thirty years ago. This gain in height and weight was observed some years ago in children born in the 1920's. Drs. Hundley and Mickelson of the Public Health Service have found this trend to be continued, at least as late as 1949, in their recent comparison of the height and weight records of seven to nine-year-olds in Philadelphia.

In sum, the high nutritional level of the American people is due to the fortunate interplay of medical science, food technology, education and the national economy. Improvement of the average diet has built stronger Americans, saved lives, and virtually eliminated such once-prevalent deficiency diseases as pellagra, rickets, and infantile scurvy. It has played an important part, along with public health measures, in the decline of tuberculosis.

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Special Article

Present Status of Prediabetes

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"Prediabetes" indicates the state of a person during the period before he or she becomes plainly and clinically diabetic. There exists then a latent abnormality which may show itself under certain specific conditions. There are other people without symptoms but with gross carbohydrate abnormality, exemplified by a hyperglycemia which is discovered accidentally. These subjects are not prediabetic—they are diabetic, albeit only "chemically."

OBSTETRIC MANIFESTATIONS

Authorities from different parts of the world have confirmed the high frequency of overweight babies[1-20] and of late fetal or neonatal death ("perinatal" loss). There seems to be general agreement that the perinatal loss in prediabetic years is around 15 to 20 per cent, rising to 30 to 50 per cent in the two to five years immediately preceding the diagnosis of diabetes. Several analyses make it clear that an excessive fetal wastage may be present twenty or more years before overt diabetes appears.

A few workers, however, have found no evidence for an increased fetal loss before the appearance of diabetes. Thus Pirart,[19] in Brussels, observed no "significant differences" from the general perinatal mortality in the past histories of 502 diabetic mothers, while Wilkerson,[21] in Boston, in a "prospective" study found only ten perinatal deaths in 182 pregnancies in women who had previously been diagnosed as prediabetic. The explanation of these discrepant findings is not clear.

Not all future diabetic mothers bear large babies or stillborn babies, even if they have many children. In our series 62 per cent of mothers in their prediabetic years claimed to have produced at least one baby weighing over ten pounds at birth. Furthermore there is no apparent relation between gigantism and viability of the child; in fact, there is some evidence that the smaller babies (of diabetic mothers) are less viable.[22]

Further obstetric associations of prediabetes have been claimed to include infertility, repeated miscarriages, toxemia of pregnancy, hydramnios, prematurity, and congenital malformation in the fetus; excessive lactation, and puerperal weight gain in the mother. Prediabetes, as we have indicated,[23] may account for some "unexplained stillbirths"; it is important to establish whether it also accounts for some severe and otherwise unexplained congenital anomalies. Hoet[24] thinks that it may cause at least 30 per cent of these, as judged by abnormalities in maternal glucose tolerance.

We believe that glucose tolerance is not impaired in a completely normal person during pregnancy, or that any impairment is so slight as to be unimportant.[8,26] Consequently, an apparently "temporary" diabetic state or significant impairment of sugar tolerance during pregnancy indicates a state of potentially permanent diabetes in the mother. In such a case, the pregnancy has brought to light the prediabetic state. This is frequently more poignantly indicated by the resulting fetus being large or stillborn.

TYPE OF DIABETES WITH RELATION TO EMBRYOPATHY

Although the mild obese diabetic and the severe ketosis-prone diabetic are very different clinically, both have the same obstetrical complications and their fetuses are subject to the same embryopathy both in their prediabetic and their overtly diabetic years. The basic similarity between these two types of diabetic is further shown by their similar modes of inheritance, their appearance together in the same family, and the proneness of both types to the same degenerative vascular disease.

It has also been demonstrated that diabetic and prediabetic men father, on the whole, larger babies than do nondiabetics.[8,19,26] This larger size of the babies of such fathers is by no means as striking as in the case of mothers. Thirty-one per cent of babies of prediabetic mothers were over ten pounds in my series; 10.7 per cent of babies of (pre)diabetic fathers; and 3.7 per cent of babies of normal parents. Its practical importance is slight, since the presence of diabetes in the father has no ill effect on fetal survival.

OTHER RELATIONSHIPS OF PREDIABETES

Since diabetes is a hereditary disease (probably by

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way of a common recessive gene) prediabetes can be suspected in anyone with a strong family history of the disease, and must actually be considered to be present in certain specific instances, as when an identical twin or both parents are diabetic.

Obesity is certainly related to diabetes and prediabetes. It is plain, however, that some patients with long-standing, gross obesity have quite normal glucose tolerance curves, even when these are "sensitized" by the prior administration of cortisone.[27] This supports the suggestion that obesity produces diabetes only in subjects whose pancreases are already relatively insufficient. Richardson reached the same conclusions.[28] It must be admitted that not all authorities would agree with this interpretation. Thus Levine[29] suggests that obesity with its excessive food intake calls forth an overproduction of insulin which later leads to exhaustion of the beta cells from overwork. The conception of beta cell damage from overstimulation is, however, nebulous and lacking in direct supporting evidence.

So-called "temporary diabetes"—diminished sugar tolerance or even gross clinical diabetes—may be seen in patients suffering from acromegaly, Cushing's syndrome, hyperthyroidism, severe fractures, severe burns, staphylococcal or other infections, patients undergoing treatment with glucocorticoids, or even following such a condition as myocardial infarction. When investigations have been made, it has been found that there is a high incidence of diabetes in the families of persons so affected.[33] It seems likely that the particular condition in each case merely uncovers a latent or prediabetic state. When the disorder under consideration is relieved, the glucose tolerance frequently reverts to normal. Occasionally, however, the diabetic state persists—in such a case the superadded stress state has presumably contributed enough extra damage to the already partially insufficient pancreas to render the diabetes permanent. If this conception is true, then "temporary" diabetes in these circumstances does not really exist, but patients who appear to manifest such a condition must be looked upon, followed up, and treated as prediabetics, who are liable to become obvious permanent diabetics later in life.

EFFECT ON THE FETUS

We believe that most, and probably all, of the abnormalities which occur in the fetus of the diabetic may also occur in the fetus of the prediabetic. Incidentally, we have noticed luteinization in the ovaries of the prediabetic's fetus, as has been described in the fetus of the diabetic.[30] Most interesting to us have been the islets of Langerhans. Van Beek[31] was the first to insist that enlarged islets in a stillborn fetus meant diabetes or potential diabetes in the mother. Woolf and I have confirmed this.[32] We have found the proportion of islet tissue in the pancreas of the prediabetic's fetus to be about 7 per cent, as against about 1.3 per cent in other fetuses. Furthermore, the islets appeared to contain a higher proportion of beta cells than normal, and the beta cells were unusually full of staining granules. This would seem to indicate a very high insulin content of such a pancreas—even thirty times the normal.

The causation of the embryopathy is unlikely to be hyperglycemia, since the fetal abnormalities may occur in babies of the prediabetic mother who has consistently normal blood sugar levels. Growth hormone *may* play some part, but this is by no means proved, and it is strange that acromegalics' infants are neither very large nor stillborn.[33] The "Cushingoid" appearance of the babies suggests that glucocorticoid excess or sensitivity may occur (or perhaps there is an increased placental permeability to hydrocortisone), but this is also unproved. It is tempting to think that the large islets play some part. Insulin is a growth hormone.[34,35] In fact, pituitary growth hormone will not function without insulin. It seems possible that the abnormal size of the fetus might be due to fetal insulin activity; but this would still leave unsolved the other features, and also the actual cause of the enlarged islets themselves.

Other suggested mechanisms which may explain some or all of the embryopathy include anoxia,[36] abnormal placenta, sex-hormone imbalance,[37] maternal obesity, and inheritance. It may well be that the factors responsible for the gigantism are quite different from those which cause the stillbirth (or the congenital anomalies). This would fit in with the idea that insulin may play a large part in the gigantism, while it seems unlikely that it would cause the more deleterious effects.

PREDIABETES AND VASCULAR DISEASE

There is a great deal of evidence to suggest that the underlying abnormal diabetic state exists from an early age[33]—perhaps from birth, even when clinical diabetes does not appear until much later, and sometimes maybe not at all. Does this abnormal prediabetic state include an abnormal vascular system? In other words, have we any evidence that the underlying long-standing prediabetic condition includes a state of prevasculopathy?

It seems in general reasonable to consider that diabetic vasculopathy is truly a part of diabetes;[38] that a potential diabetic inherits not only a congenitally defective pancreas but also a defective blood vasculature, particularly in certain sites. Alternatively the subclinical pan-

TABLE 1

At this stage the following table summarizes the abnormal conditions found in the offspring of diabetic mothers and fathers:

In offspring of:	Prediabetic and diabetic mothers	Diabetic fathers	Nondiabetic parents
Fetal gigantism	++++	++	+
Childhood gigantism	+[37]	0	0
"Cushingoid" fetus	++	0	0
Perinatal deaths	+++	+	+
"Continents" of Langerhans	+++	?	0
Congenital anomalies	++ (some authors) ± (other authors)	++[37] ±[46]	±
Abnormal glucose tolerance	++	++	? (presumably ± but no control series known)
Abnormal conjunctival vessels	+[47]		0
Future diabetes	++	++	±

Note that (1) where incidence is highest in diabetic mother group, factors are most likely intra-uterine; (2) where incidence is higher in diabetic father group than in the normal group, factors must be hereditary, linked to the inheritance of diabetes in some way.

creatic defect might itself have a deleterious effect on blood vessel walls, independent of hyperglycemia, and long before diabetes becomes manifest. Indeed we have perhaps been overobsessed with hyperglycemia as the primary feature of diabetes. Insulin has an action in fat metabolism which may possibly be more important than its more obvious effect on carbohydrate. Might it perhaps have an essential protective effect on blood vessel walls? A future diabetic might be born with a relatively inefficient beta cell mechanism—not so defective that our rough yardsticks of definition based on glucose tolerance can detect it, but bad enough so that throughout the years certain blood vessels in certain places become progressively damaged. Certainly a poorly controlled diabetic subject continues increasingly to damage his already defective vasculature, while careful control helps partially to protect it from further deterioration. If this is true one could not, in fact, expect insulin or other means of control of diabetes entirely to prevent vascular disease, since the vessels are already damaged by the time diabetes is diagnosed.

IS PREGNANCY DIABETOGENIC?

Pregnancy can plainly be considered to be diabetogenic to the mother, at least as long as it lasts.[30] The question of importance is whether the diabetogenic action has a permanent effect—in other words, whether the pregnancy predisposes to the appearance, or earlier appearance, of clinical diabetes. Evidence that pregnancy is thus truly diabetogenic includes the facts that the incidence of diabetes is higher in married women than single,[40,41] that it rises with increasing parity,[42] and that it is very high among women who have borne ten or more children.[43]

Next we must inquire whether pregnancy is diabetogenic for the child in the presumed abnormal internal environment of a diabetic or prediabetic mother. One certainly wonders whether the grossly hypertrophied islets of Langerhans in the infant do not suggest permanent damage. If this is so then the children of diabetic mothers should have a greater tendency to diabetes than the children of diabetic fathers. Boulin[44] claims to have found this, but it does not appear in the more satisfying figures published by Steinberg.[45]

DIAGNOSIS

If prediabetes is suspected on the basis of some of the features discussed above, or on other grounds of which space does not permit discussion (e.g., repeated attacks of pancreatitis, angina pectoris in a premenopausal woman, cancer of body of uterus), an attempt should be made to establish a firmer diagnosis.

The ordinary glucose tolerance test may be useful, in which particular attention is paid to the two-hour level, as I have previously discussed in detail.[8] Several follow-up studies have indicated the value of these figures.[21,48–50] Certainly, not all prediabetics will be detected by these means, and Fajans and Conn[51] have introduced the augmented (cortisone) glucose tolerance test for the purpose of adding extra stress to the pancreas. They

used this test particularly for finding latent diabetics in families with known diabetic members. Conn,[40] West,[82] German[27] and Duncan[68] have reported further results and modifications. We have been using this test for some time and our results (not yet published in full) may be summarized:

1. The mean rise in the tolerance curve after administration of cortisone in apparently normal people over forty-five years of age is higher than in those under forty-five (confirming West's finding).

2. The mean rise in normal pregnant women is higher than in nonpregnant controls.

3. A proportion of mild diabetics show no rise at all after cortisone.

4. A high proportion of patients who are almost certainly prediabetic (on obstetric grounds and/or on account of both parents or an identical twin being diabetic) give negative responses.

It would therefore appear that although this test may be of some value in indicating the potential diabetic, it frequently fails to do so, whereas in older people or during pregnancy it may appear falsely positive unless the criteria of abnormality are raised.

Perhaps the very best indication of prediabetes in a mother is the finding of enlarged islets ("continents") of Langerhans in the pancreas of her stillborn infant. Woolf and I[82] have shown that, if the mother is not a known diabetic, and if the infant is not erythroblastotic, maternal prediabetes can confidently be diagnosed.

PREDIABETES AND PROPHYLAXIS

The study and diagnosis of prediabetes is not of academic interest only. It is helping us to understand the meaning and natural history of diabetes, some aspects of its genetics, where best to look in search of new diabetics, factors in the development of the overt disease, the importance of so-called "temporary" diabetes, and the cause of certain stillbirths. From the point of view of the patient and the child, can its diagnosis be of value in prophylaxis?

In view of the dangers to the infant of the prediabetic, we now recommend that management of the mother's parturition and of the newborn infant should be the same as with an established diabetic.[3]

Hoet goes further,[34] and uses insulin during pregnancy in his suspected prediabetics, even though there is no real hyperglycemia. His dosage rises during the course of gestation to 60 or 80 units daily, according to the mother's tolerance. He claims to prevent miscarriages, stillbirths and congenital malformations. Thus the "pregnancy wastage" in his series before treatment was thirty-five out of sixty-nine, whereas eighteen subsequent pregnancies in the same mothers which were carefully managed by him all ended with live newborns. Such results are impressive, but it is unfortunate that he presents no control series.

The most obvious abnormality to treat in many prediabetics is obesity. A diet of 800 calories a day or thereabouts is frequently necessary. If loss in weight is sufficient to prevent the onset of overt diabetes it is not unreasonable to believe that it also at least delays the vascular degeneration.

The actual diet to be recommended to prediabetics in general is controversial at the present time. Perhaps they, par excellence, should have a low saturated fat intake.

Further, if our belief regarding the presence of "diabetes from birth" is true, it is surely plain that insulin given only when overt carbohydrate defects are present would not be expected to prevent a vascular lesion which has already been developing for a long time. If we could give insulin early in the prediabetic phase, might we not then prevent the vascular disease? This, of course, is not known, but it is worth considering.

One may even wonder whether the oral sulfonylureas might have any place in prophylaxis. Whatever their exact mode of action, they do not seem to cause any damage to the pancreas, and may even aid in beta cell regeneration, according to the studies of Gepts.[54]

It must be plain that there is still a great deal to be learned about prediabetes—at least we know that it is not just a sterile and academic subject, but one of considerable importance from many practical and theoretical angles.

SUMMARY

The author's concepts of the meaning, relations, diagnosis and practical significance of prediabetes are considered in this article. The embryopathy of the infant of the prediabetic mother appears to be exactly similar to that occurring in the infant of the established diabetic. Among other facets of prediabetes it would be particularly important to know what is happening to blood vessels in this phase—does prediabetic vascular damage occur?

The diagnosis of prediabetes usually depends upon, first, suspicion, then glucose tolerance, with the final proof of overt diabetes later. The place of "augmented" glucose tests is not yet clear. The main practical applications arising from the diagnosis lie in the management of the perinatal period in future pregnancies and in dietary restriction where necessary.

SUMMARIO IN INTERLINGUA

Le Stato Presente de Prediabete

Prediabete es definite como un stato de latente anormalitates que se manifestara, sub certe conditiones, in le signos e symptomas de ver diabete clinic. Un subjecto in qui hyperglycemia sin symptomas evidente es discoperite accidentalmente non es prediabetic sed diabetic.

Es discutite le signification de prediabete pro graviditate e parturition, tanto pro le matre como etiam pro le feto. Le autor opina que in iste respecto le factos establite pro diabete es potentialmente valide pro prediabete. Ille assere que pregnantias es diabetogene, i.e. capace a avantiar prediabete al stato de diabete clinic.

Es discutite le pathologia vascular associate con diabete, con le presentation del these que iste pathologia es initiate durante le stadio prediabetic que alora debe esser traciate in retro usque al vita prenatal del individuo.

Le diagnose de prediabete remane controverse. Le mesmo vale pro le prophylaxe. Le autor summarisa su presentation in asserer que su thema es non solmente de interesse theoric sed de alte importantia practic. In signalar le lacunas in nostre cognoscentias del condition designate como prediabete, le autor urge recercas additional.

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Present Status of Dietary Treatment of Diabetes

At least one author with an extensive experience with the "free" diet has advised against its use on the basis of frequent complications. G. Engleson (*Acta Paediat. 43*:389, 1954) has examined the incidence of complication in 217 cases of diabetes occurring before the age of forty at Vaxjö, and in forty-two diabetic children at Lund. Both groups had been treated during the ten years when use of the "free" diet prevailed. In the adult group, one or more major complications were found in two thirds of the patients. Only 6.5 per cent of the patients who had had diabetes for more than ten years were free of complications. The juvenile group frequently demonstrated abnormalities of liver function, and normal growth was not always achieved.

The frequency of these discouraging results led Engleson to conclude that "dietary restrictions should be observed in the management of diabetes, especially as a prophylactic measure against long-term diabetes." As in most studies of this problem, the absence of a comparable control group which was treated with dietary restrictions makes this conclusion open to question.

A survey of members of the American Diabetes Association by S. B. Beaser (*New England J. Med. 244*: 714, 1951) indicated that only a small percentage of these physicians were treating their patients by the "free" diet. In honesty it must be admitted that a high and largely undetermined percentage of the diabetic population fail to follow prescribed diets.

Much has been done to simplify and standardize dietary instructions by a joint committee of the American Diabetes Association and the American Dietetic Association (E. K. Caso, *J. Am. Dietet. Assn. 26*:575, 1950). This system of instruction has found widespread acceptance in the majority of the hospitals in the United States and the teaching resources which are available have made practical dietetic instruction possible in the physician's office.

The role of diet as a therapeutic tool has been reemphasized by two recent articles authorized by the Council on Foods and Nutrition of the American Medical Association. The first of these concerns diet in childhood diabetics (R. L. Jackson, *J.A.M.A. 168*:42, 1958), and the second deals with diabetic diets in adults (W. H. Daughaday, *J.A.M.A. 167*:859, 1958).

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Response to Cortisone in Prediabetes

Glucose- and Steroid-glucose Tolerance in Subjects Whose Parents Are Both Diabetic

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In 1952 studies by Berger[1] were published showing that subjects with normal glucose tolerance exhibited impairment of tolerance in some instances after the administration of corticotropin. On the basis of his data he concluded that nondiabetic siblings of diabetics were more likely to exhibit impairment of glucose tolerance after corticotropin than were subjects with no family history of diabetes. Subsequently, Fajans and Conn[2,3] reported studies begun in 1950 in which cortisone-modified glucose tolerance tests were performed on subjects with and without a family history of diabetes. They showed that thirty-seven subjects with normal glucose tolerance and no family history of diabetes rarely (3 per cent) exhibited venous blood glucose levels over 140 mg. per 100 ml. two hours after glucose was administered even when two doses of cortisone were administered prior to the test. On the other hand, 24 per cent of seventy-five subjects with normal glucose tolerance and a family history of diabetes (parent, sibling or child of a diabetic) exhibited two-hour glucose values over 140 mg. per 100 ml. when the cortisone-glucose tolerance test was performed. Furthermore, they showed that certain obese subjects whose glucose tolerance tests returned to normal coincident with weight loss induced by diet continued to exhibit "positive" cortisone-glucose tolerance tests. Lastly, follow-up of thirty individuals for periods of one to four years revealed that diabetes had developed in 13 per cent of those who had previously exhibited normal glucose tolerance tests and positive cortisone-glucose tolerance tests. An additional 10 per cent had developed "probable diabetes." In contrast only 2 per cent of the group of forty-one with initially negative cortisone-glucose tolerance tests developed diabetes during a similar period, and none in the latter group had developed "probable diabetes."[3]

These findings of Fajans and Conn suggested the possibility that individuals who have normal glucose tolerance tests and "abnormal" cortisone-glucose tolerance tests might be prediabetic and furthermore, that the incidence of susceptibility to diabetes in individuals with negative cortisone-glucose tolerance tests might be significantly less than in the general population. Since the development of a reliable test for "prediabetes" would be extremely helpful in the investigation of the nature of diabetes, it seemed of great importance to explore further the reliability of the cortisone-glucose tolerance in predicting the eventual development of diabetes.

Since the incidence of prediabetes is very much higher in nondiabetic subjects whose parents are both diabetic than in subjects with no family history of diabetes or in those with a single diabetic sibling, parent or child,[4,5] the responses to a prednisone-glucose tolerance test of fourteen subjects with two diabetic parents were examined by the author.[6] No detectable differences were found between the responses of the latter group and the responses of a group with a single diabetic parent, sibling or child. Furthermore, the responses of those whose parents were both diabetic were only slightly greater than that of a group with no family history of diabetes. For these reasons we were unable to show with certainty that "prediabetics" are unusually responsive to prednisone. The 10 mg. doses of prednisone employed were slightly more potent in producing hyperglycemia than were 50 mg. of cortisone.

The present studies were designed to determine whether or not the hyperglycemic responses to cortisone of nondiabetic individuals whose parents are both diabetic are significantly greater than those of a control group with no family history of diabetes. Since all or almost all the subjects with two diabetic parents would be prediabetic[4,6] and very few or none of the control group would be prediabetic this seemed to be a suitable method of determining the specificity of the hyperglycemic response to cortisone with respect to

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prediabetes. In addition we have tested the response to cortisone in a group of subjects with borderline or slight impairment of glucose tolerance.

METHODS

All subjects were ambulatory and well. Measured diets were not prescribed prior to testing but each subject was interviewed and none was tested who had observed any dietary restrictions of carbohydrates or calories. Glucose was administered orally according to the technic employed by Fajans and Conn[2] (1.75 gm. of glucose per kilogram of ideal body weight). Venous blood glucose levels were determined by the method of Nelson.[7] The cortisone modified tests were also those employed by Fajans and Conn. The subjects ingested 50 mg. of cortisone acetate 8.5 hours and again two hours before glucose was administered. Subjects whose weights exceeded 160 pounds were given cortisone doses of 62.5 mg. Except for instances specifically mentioned in the text each subject had a control blood glucose two hours after oral glucose alone and one to seven days later a cortisone-glucose test was performed. A majority of the subjects, with and without a family history of diabetes, had the control glucose tolerance test followed by the cortisone-glucose tolerance test on the next day.

All the subjects tested with a family history of diabetes came to our attention through their diabetic parents or their nondiabetic siblings. None was contacted through diabetic siblings. No subjects were included in this group unless unequivocal clinical or laboratory evidence of diabetes was present in both parents. Only one of the parents did not have a history of clinical symptoms of diabetes or fasting hyperglycemia. This person had a venous blood glucose of 210 mg. per 100 ml. two hours after 100 gm. of glucose orally. The remote possibility that a parent might have nonhereditary diabetes was considered in each instance. However, no evidence was found that such entities as pancreatitis, acromegaly, or hemochromatosis existed in any of the parents. The details concerning the families studied are shown in table 1.

A cortisone-glucose tolerance test was performed in two matched groups. A group of twenty-six individuals with two diabetic parents and normal glucose tolerance were studied. Forty-four subjects with no family history of diabetes and normal glucose tolerance served as a control group. The control subjects were students, technicians, doctors, volunteer workers, spouses of diabetics, etc. The mean and range for age and for weight in this group was thirty-two years (sixteen to fifty-five) and 152 pounds (108-220). In the group with two diabetic parents these values were thirty-seven years (fifteen to fifty-seven) and 156 pounds (115-230). There were sixteen females and ten males in the group with two diabetic parents. In the control group there were nineteen females and twenty-five males. (In neither group was there a significant difference between the responses of males and females with respect to the response to glucose or cortisone-glucose.) No subject was included in either of these latter groups whose blood glucose exceeded 115 mg. per 100 ml. two hours after oral glucose.

Certain other individuals with two diabetic parents were not included in the group which was compared to the control group because they did not have both a cortisone-glucose tolerance test and a normal glucose tolerance test. Details covering these forty-one persons are also shown in table 1.

RESULTS

The details concerning each of ten families in which both parents were diabetic are recorded in table 1. The status of all offspring who survived beyond childhood is recorded (sixty-seven individuals, sixty-six living). The mean age of these individuals was thirty-eight years (range fifteen to fifty-seven). Three additional children died at birth or in infancy and in one child death was due to an accident at age twelve. The age at which diabetes had been found in the parents ranged from twenty-eight to seventy-four. No attempt was made to determine the onset of symptoms or signs of diabetes in the parents and it may be assumed that in most instances the onset of impairment of glucose tolerance had occurred many months or years before the diagnosis was made.

Glucose tolerance in subjects whose parents were both diabetic. The data with respect to the glucose tolerance of the sixty-six living individuals whose parents were both diabetic may be summarized as follows: In eighteen persons no information was available concerning glucose tolerance. In the remaining forty-eight in this group of sixty-six the status of glucose tolerance was known since these latter persons had had either a glucose tolerance test (forty-two individuals), or known clinical diabetes (five individuals), or fasting hyperglycemia (152 mg. per 100 ml. in one individual). Of those offspring of two diabetic parents who had never exhibited fasting hyperglycemia eight had two-hour glucose values exceeding 115 mg. per 100 ml. Thus a total of fourteen (29 per cent) of the forty-six individuals whose status of glucose tolerance was known had impairment of glucose tolerance.

Mosenthal and Barry[8] suggested that subjects whose

TABLE 1

Status of individuals whose parents were both diabetic

Ages, and ages at diagnosis of diabetes in parents	Subject	Age	Sex	Two-hour glucose in mg./100 ml.	Two-hour glucose in mg./100 ml. after glucose and cortisone	Remarks
Father 74, diag. 65. Mother died 67, diag. 52.	HEC	42	F	100	156	
	MER	49	F	60	74	
	OEF	38	F	56	114	
	TEW	35	F	84	114	
	JE	37	M	108	120	
	WE	44	M			diabetes at age 33
	REO	41	M			not tested
	AE	31	M			not tested
Father died 60, diag. 58. Mother 57, diag. 57.	FL	21	F	100	92	
	LL	33	F	80	136	
	CLA	31	F	76	116	
	CAL	15	F	74	120	
	DL	26	M	108	120	
	CHL	29	M	96	128	
	KL	28	M	128	142	
Father died 64, diag. 56. Mother 60, diag. 54.	JG	35	M	117	154	
	AG	21	F	100	168	
	ALG	24	M	87	120	
	IJG	30	M	94	83	
	DG	27	M	98	138	
	DGT	39	F			not tested
	TGC	36	F			not tested
	GG	23	F			not tested
Father 58, diag. 56. Mother 55, diag. 28.	LSD	23	F		108 (Prednisone)	
	LSS	21	F		92 (Prednisone)	
	JSS	36	F			not tested
	ESM	34	F			not tested
	DS	26	M			not tested
Father 75, diag. 57. Mother 66, diag. 66.	JM	50	M		92	
	NMV	30	F		102	
	MMS	33	F		100	
	CM	43	M		118	
	AMS	47	F			not tested
	AM	35	M			not tested
	SM	45	M	106		
	EM	31	M			not tested
	JMS	35	F			not tested
	BM	30	M	158	131	
Father 79, diag. 74. Mother 73, diag. 72.	CB	50	M	103	125	
	EBH	35	F	137	209	history pos. G.T.T.
	NBL	57	F	80	109	
	OB	41	M	68	90	
	DBB	52	F	109	123	
	FBR	47	F	97	102	
	DB	55	M			diabetes
	RB	47	M			diabetes at age 39
	IB	39	M			not tested
Father 74, diag. 70. Mother 68, diag. 63.	ANG	30	M		84 (Prednisone)	
	BLG	42	M			not tested
	JG	40	M			not tested
	NAG	35	M			not tested
Father 79, diag. 69. Mother 73, diag. 69.	MBW	37	F	160	157	history pos. G.T.T.
	EBW	53	F	50	214	
	CB	55	M	83	206	
	BB	29	M	65	73	
	CB	40	M	124	118	
	MBE	34	F	100	134	
	EBM	52	F			not tested
	CWB	48	M			diabetes at age 45
Father 69, diag. 58. Mother 63, diag. 49.	EO	40	M	208	184	
	ETM	45	F	115	160	
	MTJ	42	F	163	220	
	ET	44	F			fast. B.G. 152
	EOT	34	M			not tested
	JTS	38	F			died rh. heart
Father 72, diag. 58. Mother died 56, diag. 40.	EM	43	F	92	116	
	HM	43	M			diabetes at age 22

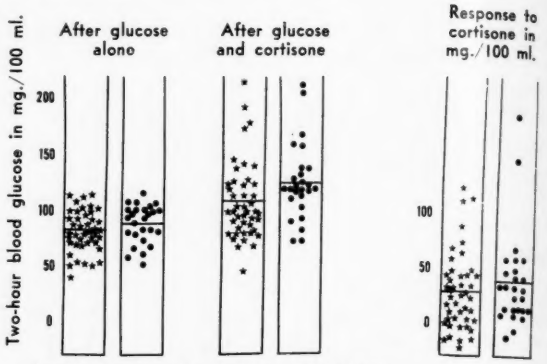
two-hour glucose levels exceeded 100 mg. per 100 ml. had impairment of tolerance. By these criteria (which when applied probably lead to the inclusion of some normals in the "diabetic" group) 40 per cent of those whose glucose tolerance was known were "diabetic."

Cortisone-glucose tolerance in individuals whose parents were both diabetic. The data in figure 1 show that the administration of cortisone resulted in an elevation of the two-hour blood glucose in the forty-four *control* subjects with *no* family history of diabetes. The mean elevation produced was 28 mg. per 100 ml. The hyperglycemic effect of cortisone was determined in each individual by comparing the two-hour blood glucose after glucose alone with the two-hour blood glucose when the test was repeated after cortisone. The mean response (35 mg. per 100 ml.) of those with two diabetic parents was slightly higher than that of the control group. However, the responses of the two groups were not significantly different ($p>0.4$). An examination of the scatter of the data reveals no tendency for the data to cluster into clearly separated groups which might be interpreted as "negative" or "positive" reactors.

It is also apparent from the data in figure 1 that the incidence of "positive" cortisone tests (two-hour glucose over 140 mg. per 100 ml.) in the subjects whose parents were both diabetic is no greater than in the control group. In the control group the incidence of "positive" tests was 18 per cent while in those with two diabetic parents it was 19 per cent.

Four additional individuals whose parents were both diabetic were available for only one day and were therefore tested with the cortisone-glucose tolerance test only (table 1). These results were not included in figure 1 since control tests with glucose alone were not done. These subjects had two-hour blood glucose levels of 92, 100, 102, and 118 mg. per 100 ml., respectively, after cortisone and glucose. Three other similar subjects had two-hour glucose levels after prednisone and glucose of 84, 92, and 108 mg. per 100 ml., respectively. The two 10-mg. doses of prednisone administered had been found previously to be slightly more potent than two 50-mg. doses of cortisone acetate in producing hyperglycemia under these conditions.[4] Thus a total of seven additional subjects with two diabetic parents were tested with steroid-glucose tolerance tests and none exhibited responses which were unusually great.

It is of interest that in both the control groups and the groups with two diabetic parents every individual who exhibited "positive" responses was either older



★ Subjects with no family history of diabetes.
• Subjects with both parents diabetic.

FIG. 1. Responses to the cortisone-glucose tolerance test in subjects with no family history of diabetes and in those whose parents were both diabetic. In the pair of columns on the far right are presented the responses to cortisone. This response was the difference between the two-hour blood glucose after glucose alone and the two-hour blood glucose after both glucose and cortisone.

than the mean of the group (effect of age?) or if not, he or she had received a greater dose of cortisone per kilogram than average. (It may be noted that according to the technic of Fajans and Conn the dose is only crudely adjusted for weight. Subjects receive 50 mg. doses of cortisone acetate unless weight exceeds 160 pounds in which case 62.5 mg. is administered.)

Cortisone glucose tolerance in subjects with slight impairment of glucose tolerance. Since it seems likely that individuals with minor abnormalities of glucose tolerance would be prone to develop clinical diabetes we have evaluated the response to the cortisone-glucose tolerance test in a group of these individuals. Table 2 shows the responses of twenty-six such subjects. Many of these subjects have high two-hour values after cortisone and glucose; however, it is important to note that in the group as a whole, the high levels are not attributable to unusually great responses to cortisone. The responses of these individuals to cortisone (mean of 20 mg. per 100 ml.) were no different from those of our control group (mean of 28 mg. per 100 ml.) or those of the subjects of German[9] with no family history of diabetes (20 mg. per 100 ml.).

Effect of one week of hydrocortisone therapy in normal young males. Previous studies of the author[6] suggested that older subjects might be more responsive to the hyperglycemic effects of corticosteroids. However, the data were not adequate to show this conclusively. More recently we have studied the effects of hydrocortisone in five healthy young subjects from

TABLE 2

Cortisone response in subjects with borderline or slightly abnormal glucose tolerance

Subject	Age	Sex	Two-hour glucose in mg./100 ml. after glucose alone	Two-hour glucose in mg./100 ml. after cortisone and glucose	Response to cortisone in mg./100 ml.
1	50		127*	119*	—8
2	24		152*	211*	59
3	23		124*	145*	21
4	38		122*	124*	2
5	33		139*	132*	—7
6†	50		126*	113*	—13
7			164*	192*	28
8†	38	F	142	192	50
9†	44	F	124	187	63
10†	47	F	120	114	—6
11	31	M	114	124	10
12	46	F	115	120	5
13	55	F	112	100	—12
14	22	F	113	180	67
15	35	F	168	135	—33
16	41	M	136	104	—32
17	43	F	124	166	42
18	28	F	124	156	32
19	28	F	124	166	42
20‡	23	M	128	142	14
21‡	35	M	117	154	37
22‡	37	F	160	157	—3
23‡	40	M	124	118	—6
24‡	35	F	137	209	72
25‡	42	F	163	220	57
26‡	45	F	115	160	45
Mean	37				20

*Subject of Goudie, et al.,[21] blood glucose by Folin-Wu method.
†Family history diabetes.
‡Both parents diabetic.

twenty-one to twenty-five years of age. Hydrocortisone, 40 mg. each eight hours, was administered for one week. In each subject an intravenous glucose tolerance test was performed before therapy and eight hours after the last dose. There was no significant change in tolerance in any of the five subjects. The fasting blood glucose of each individual was slightly elevated (4-15 mg. per 100 ml.) eight hours after the first dose of 40 mg. of hydrocortisone even though glucose tolerance after one week of therapy was unchanged.

DISCUSSION

At present it is not possible to be certain concerning the incidence of the eventual development of diabetes in subjects whose parents are both diabetic. The data of Steinberg[4,5] are compatible with the notion that the incidence would approach or reach 100 per cent if the individuals lived to old age. Since diabetes is more likely to occur in the fifth, sixth and seventh decade than at any earlier time the fact that only about one third of our subjects, whose ages average thirty-seven years, have impairment of glucose tolerance does not exclude the possibility that they are all genetically prone to diabetes. Less than one third of the diabetics observed at the Joslin Clinic experienced the onset of diabetes before age forty.[10] Studies based on most of the diabetic population in the area of Oxford, England by Pyke[11] showed that about three quarters of those who had developed diabetes had done so after age forty. It would seem likely then that in our group of individuals whose parents were both diabetic and whose ages averaged thirty-seven years, if every individual were genetically prone to diabetes, between 10 and 40 per cent of the group would have exhibited evidence of diabetes (depending on the criteria employed to make the diagnosis).

Fasting hyperglycemia was already present in one or more children in six of these ten families. Twenty-nine per cent of those whose status of glucose tolerance had been tested in this or other laboratories had abnormal tolerance. Furthermore, 40 per cent of this group of forty-eight with an average age of thirty-seven years had abnormal glucose tolerance by the standards of Mosenthal and Barry.[8] In view of the above it would appear that our findings are compatible with the notion that eventually the incidence of diabetes will approach 100 per cent in those who survive to old age.

In view of the fact that those whose parents were both diabetic did not exhibit unusual responses to cortisone or prednisone it seems unlikely that this test can identify with any appreciable accuracy the presence of genetic susceptibility to diabetes. Furthermore, the subjects who already exhibited slight impairment of tolerance showed no evidence of increased responsiveness to cortisone (table 2).

We considered some other possible explanations for the occurrence of a "positive" cortisone-glucose tolerance test after a normal response to glucose alone. Our data and those of German[9] show that the magnitude of the apparent response of the two-hour glucose to cortisone is highly variable. For example, the responses of our control subjects ranged from minus 23 to plus 121 mg. per 100 ml. We believe this is mainly attributable to the intra-individual variability of the two-hour glucose from day to day when oral glucose is administered. We did not perform duplicate control tests on these subjects but in another group of thirty-four nondiabetic subjects on a fixed hospital diet prior to testing, to whom we administered 50 gm. of glucose orally on two occasions, mean intra-individual variation of the two-hour glucose was 18 mg. per 100 ml. (range of 1 to 50 mg. per 100 ml.). The author analyzed the

data of Unger[12] who had administered 100 gm. of glucose orally on two separate occasions to each of thirty-three ambulatory individuals. In subjects with normal fasting blood glucose values and two-hour values below 116 mg. per 100 ml. there was a mean intra-individual variation of 20 mg. per 100 ml. with a range of 1 to 80 mg. per 100 ml. In sixteen additional subjects with normal fasting values and two-hour levels over 116 mg. per 100 ml. the mean intra-individual variation was 37 mg. per 100 ml. with a range of 0-85 per 100 ml. Freeman et al.[13] had previously demonstrated and quantitated the intra-individual variability of oral glucose tolerance tests in subjects observing standard institutional diets.

This moderate variability of response to orally administered glucose makes it difficult to interpret the results of a pair of tests in which one test is a control glucose tolerance test and the other a cortisone-glucose test.

A "positive" cortisone-glucose tolerance test (two-hour glucose above 140 mg. per 100 ml.) would occur less frequently of course among individuals with "low normal" glucose tolerance and more frequently in those with "high normal" glucose tolerance.

Since older subjects have poorer glucose tolerance[14-17] one would expect a higher incidence of "positive" cortisone tests in this group although adequate direct evidence on this point is lacking. It is of interest that the control subjects of Fajans and those of the author are slightly younger than the groups with which they were compared. Jackson[18] found a higher incidence of "positive" cortisone-glucose tolerance tests in older subjects. The ages of thirty-seven control subjects of Fajans and Conn were not given; however, the mean age of a group of fifty subjects from which they were selected was twenty-eight years. It seems likely that the low incidence of "positive" cortisone-glucose tolerance tests in their controls (3 per cent) was at least partially attributable to the youth of the group. In the studies of Moyer and Womack[19] and those of Mosenthal and Barry[8] there are insufficient data concerning subjects over fifty years of age to allow any conclusions concerning normal two-hour glucose values for persons over fifty. However, Unger[12] tested healthy individuals (food handlers) many of whom were middle-aged. Two hours after 100 gm. of glucose by mouth the mean blood glucose (Somogyi-Nelson) of his twenty-three subjects from fifty to fifty-nine years of age was 132 mg. per 100 ml. If these individuals were tested again after cortisone and exhibited average responses to the drug one would have to assume that the majority of these normal subjects would have "positive" cortisone-glucose tolerance tests!

That younger subjects may be less responsive to the hyperglycemic effects of corticosteroids is suggested by the fact that our normal young males showed no evidence of impaired glucose tolerance after one week's therapy with hydrocortisone. In contrast, Bastenie[20] had shown previously that after one week of therapy with comparable doses of cortisone (1 gm.) glucose tolerance was regularly impaired in patients with a variety of disorders. Those subjects were presumably older than our subjects and this may account for the differences between the responses of the two groups although other factors may have been responsible.

Jackson[18] has been impressed with the frequency of "negative" cortisone-glucose tolerance tests in those individuals who are very likely to become diabetic. German[9] failed to find any evidence that the hyperglycemic responses to cortisone in obese patients were greater than usual even though obese subjects are much more likely to develop diabetes. Goudie, Stamm and Dische[21] found that subjects who had glycosuria on screening were not unusually responsive to cortisone (technic of Fajans).

The fact that our findings fail to indicate that persons with prediabetes are unusually responsive to cortisone under these conditions does not necessarily exclude the possibility that administration of a corticosteroid for a longer period might identify individuals with impaired "reserve" of beta cell function.

SUMMARY

Subjects whose parents were both diabetic were studied with respect to glucose tolerance and cortisone-glucose tolerance. The status of glucose tolerance was known or tested in forty-six of these individuals whose ages averaged thirty-seven years.

In fourteen (29 per cent) glucose tolerance was impaired. These data were compatible with the notion that the incidence of genetic susceptibility to diabetes in this group approaches 100 per cent.

Cortisone-glucose tolerance tests were performed in twenty-six persons with normal glucose tolerance whose parents were both diabetic. Their responses to cortisone were not significantly different from those of a control group with normal glucose tolerance and no family history of diabetes. Seven other subjects whose parents were both diabetic were not tested after glucose alone, but had steroid-glucose tolerance tests. Four had cortisone-glucose tolerance tests and three had prednisone-glucose tolerance tests. The results of all seven tests were normal.

Cortisone-glucose tolerance tests were performed in twenty-six subjects with slight impairment of glucose tolerance. Their responses to cortisone were normal.

These findings suggest that individuals with prediabetes are not unusually responsive to the hyperglycemic effects of cortisone when it is administered by the technic of Fajans and Conn.

SUMMARIO IN INTERLINGUA

Le Responsa a Cortisona in Prediabete: Tolerantia pro Glucosa e pro Glucosa e Steroide in Subjectos a Patre e Matre Diabetic

Subjectos de qui ambe le parentes esseva diabetic esseva studiate con respecto a lor tolerantia pro glucosa e pro cortisona e glucosa. Le stato del tolerantia pro glucosa esseva cognoscite o determinate in quarantasex de iste individuos qui habeva un etate medie de trenta-septe annos.

In dece-quatro (29 pro cento) le tolerantia pro glucosa esseva vitiate. Iste datos esseva in congruentia con le notion que le incidentia de susceptibilitate genetic pro diabete in iste gruppo esseva proxime a 100 pro cento.

Tests de tolerantia pro cortisona e glucosa esseva effectuate in vinti-sex subjectos in qui le tolerantia pro glucosa esseva normal sed de qui le duo parentes esseva diabetic. In iste gruppo le responsa a cortisona non differeva significativemente ab le correspondente valores in un gruppo de controlo con normal tolerantia pro glucosa e nulle antecedentes familial de diabete. Septe altere subjectos de qui le duo parentes esseva diabetic non esseva studiate con glucosa sol, sed in illes tests de tolerantia pro steroide e glucosa esseva effectuate. In quatro cortisona e glucosa esseva usate, in tres prednisona e glucosa. In omne iste septe subjectos le resultatos esseva normal.

Tests de tolerantia pro cortisona e glucosa esseva effectuate in vinti-sex subjectos in qui le tolerantia pro glucosa sol esseva levemente vitiate. Le responsas a cortisona esseva normal.

Le observationes pare indicar que subjectos con prediabete non es inusualmente responsive al effecto hyperglycemic de cortisona quando illo es administrate per le technica de Fajans e Conn.

ACKNOWLEDGMENT

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ADDENDUM

Since the preparation of this manuscript, an additional subject of particular interest has been tested. Both parents of this twenty-eight-year-old healthy female are diabetic and birth weights of her two children were ten pounds and nine pounds. She represents the eleventh such family we have studied. Her blood glucose two hours after oral glucose was 66 mg. per 100 ml. After cortisone and glucose it was 97 mg. per 100 ml.

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The Effect of Prior Carbohydrate Intake on the Oral Glucose Tolerance Test

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Although starvation can produce decreased tolerance to glucose, sometimes called "hunger" diabetes, clinicians differ regarding the extent and necessity of dietary preparation of the patient before an oral glucose tolerance test for diabetes. Some advocate at least three days' preparation with a minimal daily carbohydrate intake of 300 gm.; others recommend a daily intake of 200 gm., while many feel that no preparation is necessary to obtain a valid test in the apparently well-nourished individual.

In 1940, Conn[1] attempted to quantitate the phenomenon of decreased glucose tolerance following restricted diets, by placing a group of nine volunteers on special diets prior to glucose tolerance testing. First, the group was given a high carbohydrate diet for three days consisting of 300 gm. of carbohydrate in a daily diet of 3000 calories. Glucose tolerance tests followed and showed normal glucose tolerance curves for all subjects. Next, the daily diet was restricted to 20 gm. of carbohydrate, 1600 calories for five days. Repeat glucose tolerance tests showed a marked decrease in glucose tolerance with three undernourished subjects having the greater abnormalities. On the basis of his study, Conn suggested that an inadequate carbohydrate diet before testing might result in false-positive reactions for diabetes, while a prior intake of 300 gm. of carbohydrate in a daily diet of 3000 calories would preclude such reactions. However, Conn did not determine what level of carbohydrate intake was necessary to restore to normalcy the glucose tolerance that had been impaired deliberately by the restricted 20 gm. carbohydrate 1600-calorie diet.

We therefore undertook a study of the problem to determine whether glucose tolerance of healthy individuals, if impaired by drastically restricted carbohydrate intake, could be restored to normalcy by as little as 150 gm. of carbohydrate intake. Since the standard dietary preparation (300 gm. of carbohydrate) often imposes hardship on such patients as pregnant women, elderly persons, and those already on other special diets, more pertinent was the question whether interpretation of glucose tolerance curves, after 150 gm. of carbohydrate intake, would be valid and would not result in a false diagnosis of diabetes or "possible" diabetes.

PROCEDURE

The study sample consisted of nine healthy male subjects aged twenty-two to thirty-seven years volunteering from a Catholic missionary order and nine healthy female subjects aged twenty-three to fifty-three years volunteering from a Massachusetts state institution.

The usual dietary pattern of each participant was obtained by a nutritionist through interview. The men averaged 311 gm. carbohydrate, 74 gm. protein, 2417 calories, and the women averaged 207 gm. carbohydrate, 66 gm. protein and 2001 calories. No subject's normal carbohydrate intake was calculated to be less than 140 gm.

A standard three-hour, 100-gm. oral glucose tolerance test was given to both men and women without prior dietary preparation. Specimens of venous blood drawn at fasting and one, two, and three hours after glucose ingestion were analyzed by the Somogyi-Nelson method.[2] The subjects were tested for glycosuria and acetonuria at each hour of the test by Clinitest and Acetest methods.

On the day following the first glucose tolerance test, the study groups were placed on a 20-gm. carbohydrate, 50-gm. protein, 1600-calorie daily diet for five days, after which the glucose tolerance tests were repeated with blood sugars analyzed in duplicate. Body weights were recorded at the inception of the diet and just

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prior to the glucose tolerance test.

All participants then were given a 150-gm. carbohydrate, 80-gm. protein, 1640-calorie diet for four days, similarly followed by glucose tolerance tests.

RESULTS

Table 1 presents, by male and female groups, individual and mean blood sugar determinations of oral glucose tolerance tests following various levels of carbohydrate intake.

Male group. After five days on 20 gm. of carbohydrate, impaired glucose tolerance was observed in all of the men. Increases were recorded at the one- and two-hour levels which averaged 140 to 125 mg./100 ml., respectively. Normal glucose removal was obtained following four days on the 150-gm. carbohydrate, 1640-calorie diets.

Table 2 shows the statistical significance of blood sugar differences observed between the various diets. Practically at all hours of blood analysis, the 20-gm. carbohydrate diet may be distinguished from the 150-gm. carbohydrate diet and the normal diet of the men. The differences indicated by "yes" are statistically significant at the 5 per cent probability level. At one and two hours after ingestion of glucose no significant blood sugar differences were observed between the normal and the 150-gm. carbohydrate diets.

Glycosuria was noted to a minor degree at various times after glucose ingestion in specimens of eight of the nine men during the glucose tolerance test following the 20-gm. carbohydrate diet. After the normal or 150-gm. carbohydrate diet, no glycosuria was evident at the time of the glucose tolerance test.

Weight loss during the restricted carbohydrate diet averaged 6.6 pounds, while weight gain during the 150-gm. carbohydrate diet averaged 1.0 pound.

Female group. Test results of the nine women followed a pattern similar to that of the men except that the glucose tolerance curves of the 20- and 150-gm. carbohydrate diets were generally higher.

Blood sugar values following the 150-gm. carbohydrate diet approached normalcy but were not restored as dramatically as they were in the men. However, the two groups experienced a similar percentage decrease in blood sugar values at the one-hour level when the 20-gm. and 150-gm. carbohydrate diets were compared (table 1).

Statistically significant differences were again ob-

TABLE 1

Individual and mean blood sugar results, mg./100 ml., following various levels of carbohydrate intake at fasting, and one, two, and three hours after glucose ingestion

	Usual carbohydrate diet*				20 gm. carbohydrate diet for five days				150 gm. carbohydrate diet for four days			
Subject	Fasting	One hour	Two hours	Three hours	Fasting	One hour	Two hours	Three hours	Fasting	One hour	Two hours	Three hours
						Male						
1	84	139	89	34	60	193	173	Clot	83	155	110	56
2	61	89	95	35	41	155	139	46	68	103	80	41
3	76	105	56	43	53	148	125	44	76	130	82	50
4	84	49	56	76	93	91	86	69	98	82	78	80
5	75	61	77	55	64	118	100	95	78	82	73	82
6	74	35	56	60	53	85	70	58	75	57	63	77
7	84	99	76	44	71	124	91	115	70	74	63	46
8	77	139	71	26	45	213	175	104	78	122	75	58
9	74	71	59	33	53	135	165	126	66	112	63	70
Mean	76	88	70	45	59	140	125	82	77	101	76	62
Standard Deviation	7.3	36.8	14.9	15.9	15.6	32.7	30.8	32.0	9.6	31.0	14.7	15.4
						Female						
1	75	71	65	39	65	166	133	75	64	119	66	34
2	74	67	71	78	63	181	200	160	65	148	145	29
3	75	72	70	69	59	161	125	111	63	109	80	40
4	75	49	81	66	63	141	130	113	55	75	65	46
5	78	80	67	47	55	155	113	57	69	145	69	24
6	78	84	95	49	71	130	135	81	70	134	109	73
7	69	95	45	63	55	276	148	69	56	131	36	36
8	75	94	55	66	67	173	107	45	63	170	36	43
9	86	101	89	91	77	219	200	155	71	144	109	76
Mean	76	79	71	63	64	178	143	96	64	130	79	44
Standard Deviation	4.5	16.4	15.7	16.2	7.2	44.8	34.2	41.2	5.7	27.3	35.0	18.5

*Calculated average carbohydrate intake: male 311 gm. and female 207 gm.

TABLE 2

Statistical significance of blood sugar differences observed between various diets
(Mean differences in mg./100 ml. and level of significance: P=.95)

Carbohydrate intakes differentiated	Fasting		Hours after glucose ingestion: One hour		Two hours		Three hours	
	Mean diff.	Significant	Mean diff.	Significant	Mean diff.	Significant	Mean diff.	Significant
			Nine males					
311 gm.* less 20 gm.	+17	Yes	−52	Yes	−55	Yes	−37	Yes
20 gm. less 150 gm.	−18	Yes	+39	Yes	+49	Yes	+20	No
311 gm.* less 150 gm.	−1	No	−13	No	−6	No	−17	Yes
			Nine females					
207 gm.* less 20 gm.	+12	Yes	−99	Yes	−72	Yes	−33	Yes
20 gm. less 150 gm.	0	No	+48	Yes	+64	Yes	+52	Yes
207 gm.* less 150 gm.	+12	Yes	−51	Yes	−8	No	+19	Yes

*Calculated average of usual carbohydrate intake.

served in the majority of comparisons between the restricted carbohydrate diet and the other two diets (table 2).

All the female participants showed glycosuria in urine specimens taken at the time of the glucose tolerance test following the 20-gm. carbohydrate diet; however, this cleared after four days on 150 gm. of carbohydrate.

Weight loss during the restricted diet averaged 3.7 pounds while weight gains during the 150-gm. carbohydrate diet averaged 2.2 pounds.

Individual Diagnoses, Male and Female. Individual glucose tolerance curves obtained have been tested against criteria for diabetes and "possible" diabetes set up in collaboration with consultants to the U. S. Public Health Service, Chronic Disease Program, Diabetes Field Research Unit. These criteria are based on a point system where venous blood sugar values by Somogyi-Nelson method (mg./100 ml.) equaling or exceeding specified levels are assigned as follows:

Time interval in relation to glucose loading	Elevated blood sugar values	Borderline blood sugar values	Diagnostic points
Fasting	110	100	1
1 hour after glucose	170	150	½
2 hours after glucose	120	110	½
3 hours after glucose	110	100	1

When data are applied to the "Elevated blood sugar values" two or more points indicate diabetes and one point indicates "possible diabetes." Lacking applicability to elevated levels two points under the "Borderline blood sugar values" indicates "possible diabetes." A case not meeting any of the above criteria is classified as "no diabetes."

On the 20-gm. carbohydrate diet none of the male participants met our diagnostic criteria for diabetes, but there were four who did meet the criteria for "possible diabetes" (table 1, Subjects 1, 7, 8 and 9). Two female participants (numbered 2 and 9) would have been considered diabetic and three others (numbered 3, 4 and 7) met the criteria for "possible diabetes."

Figures 1 and 2 graphically show composite glucose tolerance curves of male and female participants following each of the diets.

DISCUSSION

A few blood sugar values three hours after glucose seem unusually low. The blood preservative used prevents glycolysis for four days and all analyses were made from duplicate filtrates. The low values therefore are believed to be valid. Data on the clinical status of the subjects with low blood sugar values show no evidence of cause.

Blood sugar values recorded following the 20-gm. and 150-gm. carbohydrate diets may be analyzed by two different approaches.

One approach, previously discussed (table 2), is to interpret results in terms of statistical significance of increases and decreases in blood sugar values following the various diets. Using this method, it can be said first that generally the blood sugar differences between the usual and the prepared 150-gm. carbohydrate diets are not diagnostically important. Secondly, the 20-gm. carbohydrate diet differs significantly by statistical analysis from both the usual and 150-gm. carbohydrate diets for practically all blood sugar readings.

Another approach is to test the glucose tolerance curves of both diets against the diagnostic criteria for

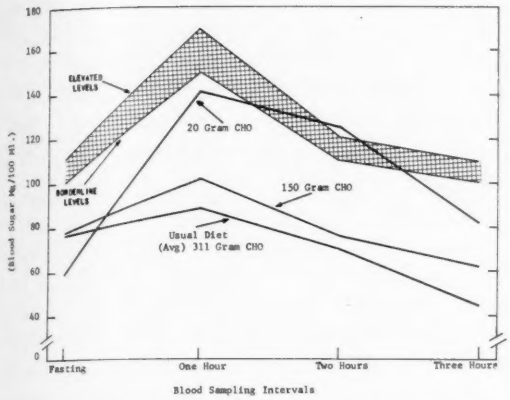

FIG. 1. Composite glucose tolerance curves by various levels of carbohydrate intake for nine males.

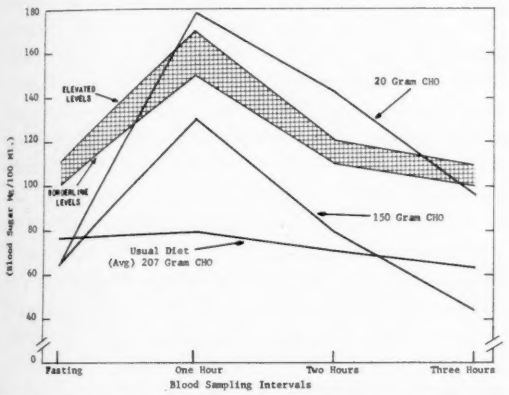

FIG. 2. Composite glucose tolerance curves by various levels of carbohydrate intake for nine females.

diabetes and "possible" diabetes used by various authorities. Table 3 shows how the subjects would have fared under varying criteria for diagnosis.[2-5] The exceptionally low carbohydrate diet impaired glucose tolerance to diagnostic levels; however, the 150-gm. carbohydrate diet restored practically all the subjects to nondiagnostic levels.

TABLE 3

Number of persons designated as having diabetes or possible diabetes, by the criteria of various authorities at different levels of carbohydrate intake

	Usual diet		20 gm. CHO diet		150 gm. CHO diet	
	Dia-betes	Possible diabetes	Dia-betes	Possible diabetes	Dia-betes	Possible diabetes
Consultants to CD Program USPHS	0	0	2	7	0	0
Conn[3]	0	0	7	6	0	2
Mosenthal and Barry[4]	0	*	10	*	1	*
Joslin Clinic[5]	0	*	8	*	0	*

*Specific criteria for "possible" diabetes not presented.

One subject, who would have been considered diabetic after the 150-gm. carbohydrate diet for four days, according to the criteria of Mosenthal and Barry,[4] had the following glucose tolerance test readings: Fasting, eighty-three; one hour, 155; two hours, 110; three hours, fifty-six. In view of the blood sugar level three hours after glucose ingestion, it could be contended that the one- and two-hour values are of borderline significance. This person is also one of the two designated as having "possible" diabetes under the 150-gm. carbohydrate diet according to Conn's criteria.[3]

A pertinent question recently asked by Conn[6] is: "What, under conditions of standard dietary preparation, is the smallest decrease in carbohydrate tolerance which can be confidently diagnosed as indicative of the presence of diabetes mellitus?" In our study, we have attempted to determine the adequacy of a low carbohydrate diet which would be practicable for most persons. The increases and decreases in glucose tolerance shown are not based on diets of long duration nor on a large study population. Therefore, the question raised cannot be completely answered by the data in this report. Findings in this study, however, do indicate that a normally nourished person may eat as little as 150 gm. of carbohydrate in a 1600-calorie daily diet for four days prior to a glucose tolerance test and the resulting glucose tolerance curve will not lead to a false diagnosis of diabetes or "possible" diabetes, using either the criteria of the UPHS consultants or those of other workers.

The actual carbohydrate intake of the general population is of practical importance in considering dietary preparation for glucose tolerance tests. An indication as to the possible carbohydrate intake of the population was obtained by the authors in a survey of 441 nondiabetic persons in a hospital outpatient clinic who were interviewed regarding their usual dietary intake. Eighty-two per cent had a daily carbohydrate intake of 150 gm. or more; 17 per cent, 100 to 149 gm.; and only 1 per cent had an intake under 100 gm. The men averaged 221 gm. while the women averaged 192 gm.

If we may then assume that most persons consume an average daily minimum of 150 gm. carbohydrate, a person requiring 150 gm. or more for normal sustenance and weight maintenance who had restricted himself to less than that requirement easily could be

isolated by inspection or brief questioning. One could be reasonably certain then that a dietary preparation as low as 150 gm. of carbohydrate daily for four days would be enough to correct the carbohydrate deficiency. Dietary preparation around this level ordinarily would not be time-consuming nor would it impose changes in the usual eating habits of the patient. These observations are similar to those offered by Irving and Wang.[6]

The point which may be emphasized here has been alluded to by Mosenthal and Barry[4] who state "the diet preceding a glucose tolerance test in nondiabetics has a profound effect on the character of the resulting curve, though a closer scrutiny of the published observations points to a probable exaggeration of this influence . . . where the crucial figure, between 50 and 125 gm. carbohydrate, lies is undetermined. However, it is scarcely conceivable that anyone who eats at all will consume less than 125 gm. of carbohydrate. On the other hand, an emaciated person will, as stressed by Conn, have a lowered carbohydrate tolerance." It is felt that this emaciated person can readily be detected by inspection or brief questioning.

We emphasize our purpose would be not to preclude any standard dietary preparation for glucose tolerance tests, but to suggest that the standard preparation requirement need not be at an unusually high level. We would suggest that a diagnostically safe minimum daily carbohydrate intake is about 150 gm.

SUMMARY

1. Eighteen healthy men and women, after showing normal glucose tolerance curves without any previous dietary preparation, were placed on a 20-gm. carbohydrate, 1600-calorie daily diet for five days. Impaired carbohydrate tolerance on the 20-gm. carbohydrate diet was observed in both male and female participants, however, only two females showed curves diagnostic of diabetes by the criteria currently used in Public Health Service diabetes studies. Carbohydrate restriction in the females produced a greater loss of carbohydrate tolerance than it did in the males.

2. In an effort to restore normal glucose tolerance, the subjects were placed on a 150-gm. carbohydrate, 1640-calorie daily diet for four days. At the end of that period, normal carbohydrate tolerance (in terms of United States Public Health Service criteria) was fully restored and none of the subjects had curves indicative of diabetes or "possible" diabetes.

3. It is believed that adequately nourished individuals need no special high carbohydrate preparation prior to administration of an oral glucose tolerance test. A minimum of 150 gm. of carbohydrate daily for four days is considered sufficient to restore normal carbohydrate tolerance in persons who have restricted their carbohydrate intake.

SUMMARIO IN INTERLINGUA

Le Effecto de Un Antecedente Ingestion de Hydrato de Carbon Super le Test del Tolerantia pro Glucosa Oral

1. Dece-octo normal homines e feminas, qui habeva monstrate normal curvas de tolerantia pro glucosa sin previe preparation dietari, esseva restringite durante cinque dies a dietas de 1.600 calorias e 20 g de hydrato de carbon per die. Vitiate tolerantias pro glucosa durante le application del dieta a 20 g de hydrato de carbon esseva observate in participantes tanto mascule como etiam feminin, sed solmente duo femininas monstrava curvas que haberea supportate un diagnose de diabete secundo le criterios que es currentemente in uso in le studios de diabete per le Servicio de Sanitate Public. Le restriction de hydrato de carbon produceva un plus marcate perdita de tolerantia pro glucosa in femininas que in masculos.

2. In le effortio de restaurar normal tolerantias pro glucosa, le subjectos esseva tractate durante quatro dies con dietas de 1.640 calorias e 150 g de hydrato de carbon. Al fin de iste periodo, normal tolerantias pro glucosa (secundo le criterios del Servicio de Sanitate Public) esseva restaurate completemente, e nulle del subjectos habeva curvas indicante diabete o mesmo le possibilitate de diabete.

3. Es opinate que adequatemente nutrite subjectos non require un preparation special a alte ingestion de hydrato de carbon ante le administration de un test oral de tolerantia pro glucosa. Un minimo de 150 g de hydrato de carbon per die durante quatro dies es considerate como sufficiente pro restaurar un normal tolerantia pro hydrato de carbon in subjectos qui ha restringite lor ingestion de hydrato de carbon.

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Sorbitol and Vitamin B_{12} Absorption

Observations on the vitamin sparing action of D-sorbitol (Morgan and Yudkin, *Nature* 180:543, 1957); (*Nutrition Reviews* 16:126, 1958) have stimulated interest in this carbohydrate as a factor influencing intestinal synthesis of vitamins (Jones and Baumann, *J. Nutrition* 66:383, 1958) and the absorption of vitamins such as vitamin B_{12} (Greenberg et al., *Nature* 180:1401, 1957) in animals. During the past year studies on vitamin B_{12} absorption have been extended to normal human subjects and to subjects suffering from pernicious anemia.

The interest of B. F. Chow and associates in the problem of factors affecting vitamin B_{12} absorption was broadened when they observed that an experimental lipotropic elixir enhanced the absorption of vitamin B_{12} in man and in the rat (*Am. J. Clin. Nutrition* 4:434, 1956). They later studied the effects of the individual components of the lipotropic elixir (B. F. Chow, P. Meier and S. M. Free, Jr., *Ibid.* 6:30, 1958) on vitamin B_{12} absorption.

In a further study (Chow et al., *Am. J. Clin. Nutrition* 6:386, 1958) the serum vitamin B_{12} levels of subjects receiving 25 μg. of vitamin B_{12} per day administered orally in a capsule containing sorbitol were found to be considerably higher after four months of treatment than those of comparable subjects receiving 100 μg. of vitamin B_{12} without sorbitol.

In every case more radioactivity from vitamin B_{12} was found in the blood, kidneys, livers, and gastrointestinal tracts of rats receiving sorbitol, indicating again the enhancing effect of sorbitol on vitamin B_{12} absorption. Pregnancy, in agreement with observations of Hellegers et al. (*Am. J. Clin. Nutrition* 5:327, 1957) also increased vitamin B_{12} absorption but not to the extent that D-sorbitol did. The results also show very clearly the shift of vitamin B_{12} from the maternal tissues to the fetus during the third trimester of pregnancy, but even here the effect of administering D-sorbitol was marked. Fetuses of mothers receiving sorbitol contained about 7 per cent of the administered radioactivity whereas those from mothers receiving no sorbitol contained only about 2.5 per cent of the administered radioactivity. This provides support for the observation of Izak et al. (*Arch. Int. Med.* 99:346, 1957) that the great fetal demand for vitamin B_{12} may lead to the development of vitamin B_{12} deficiency in the pregnant female.

From *Nutrition Reviews*, Vol. 17, No. 6, pp. 188-90, June, 1959.

The Influence of Salicylate on Hyperglycemia

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Salicylates were first observed to lower the blood sugar of diabetics at the turn of the century. However, aspirin was not used in the treatment of diabetics because it was believed that the hypoglycemic effect was the result of an hepatotoxic action of the drug.[1] More recently salicylate has been observed to reduce the glycosuria and hyperglycemia of the alloxanized[2] and partially depancreatized rat.[3] Salicylate has also been shown to increase the glucose uptake by isolated rat diaphragm.[4] Reid and McDougal[5] gave two-week courses of aspirin therapy to seven diabetics and noted in all a marked drop in blood sugar, with abolition of glycosuria. In a later study they observed a marked decrease in insulin requirement in twelve diabetics in whom salicylate was administered simultaneously with insulin.[6] Hecht and Goldner gave acetylsalicylate to twelve diabetic patients and thirteen nondiabetic patients. A significant hypoglycemic effect was obtained in most instances, and an insulin sparing effect demonstrated.[7]

Our interest in the reported hypoglycemic effects of salicylates was stimulated by the currently widespread notion that salicylate actions in many respects mimic corticosteroid actions, either by stimulation of corticosteroid production or by some other obscure mechanism. The diabetogenic effect of steroids is well known; here, then, we see an action of salicylate, namely, that on carbohydrate metabolism which is opposed to that of the steroid hormones.

In none of the previously reported clinical studies[5-7] was there any attempt at substitution of a placebo for the aspirin after a period of aspirin treatment. In our study the protocol criteria employed were very similar to those suggested as optimum by Ricketts,[8] incorporating control periods and the use of a placebo after a treatment period with the hypoglycemic agent being tested. A total of six hospitalized patients with diabetes mellitus were treated with aspirin on the wards of the Jefferson Medical College Hospital.

PROCEDURE

Upon admission to the study, treatment with insulin was discontinued and all patients were given a diet of 1800 to 2000 calories. This dietary regimen was kept constant throughout the entire study and fasting blood glucose (method of Somogyi-Nelson) and urinary glucose excretion (method of Benedict) were determined daily. Treatment was preceded by a control period I, of one week during which liver function studies (prothrombin time, serum bilirubin, cephalin flocculation, thymol turbidity), CO_2 level and basal metabolic rate (BMR) were measured. At the end of the control period an oral glucose tolerance test was performed. This was followed by the treatment period of ten days during which 6 gm. of aspirin were given by mouth daily in five divided equal doses. At the end of the treatment period, the glucose tolerance test, liver function studies, CO_2 level and BMR were measured again. In control period II (five days) placebos were substituted.

RESULTS

Results are summarized in table 1.

During treatment with aspirin, all six patients showed a marked drop in fasting blood sugar to normal or near normal levels, glycosuria disappeared, and ketonuria when present (one case) disappeared. In all cases the glucose tolerance test improved. Liver function was not impaired in any of the patients. In no case was acidosis produced. The basal metabolic rate increased in three cases and decreased in the three others. There was no appreciable weight loss during the treatment period. After cessation of the aspirin and substitution of the placebo the blood sugar rose within forty-eight hours to hyperglycemic levels of almost pretreatment magnitude. Side effects of the medication consisted of nausea, vomiting, tinnitus, and headache, and were seen in four of the six cases. These side effects were mild and did not necessitate discontinuing the drug nor did they result in decreased food intake on the part of the subjects. They subsided within twenty-four to thirty-six hours on continued medication.

DISCUSSION

The results of this and previous studies[5-7] demonstrate that aspirin lowers the blood sugar, and in diabetes reduces or abolishes glycosuria and ketonuria. In no other study has the aspirin been replaced by a placebo after the blood sugar lowering effect was demonstrated. The rapid rise in blood sugar after placebo substitution in this study suggests that psychic factors which may play an important role in the blood sugar fluctuations of diabetics were not operative in the hypoglycemic effect exerted by the aspirin.

From the Department of Medicine and Division of Endocrine and Cancer Research, Jefferson Medical College Hospital, Philadelphia, Pennsylvania.

TABLE 1

Case No.	Age	Diabetic R_x prior to admission	Weight on admission (pounds)	FBS prior to ASA* (mg. per 100 ml.)	FBS after ten days of ASA (mg. per 100 ml.)	FBS five days after ASA stopped (mg. per 100 ml.)	Weight on cessation of ASA (pounds)	BMR before ASA	BMR during ASA
1	55	Diet	142	504	164	325	141	+18	+5
2	51	None	111	285	100	185	109	+11	+18
3	45	NPH insulin 70 units daily	187	285	125	260	183	+1	—2
4	66	None	165	370	155	260	164	+11	+8
5	50	NPH insulin 15 units daily	213	520	95	300	216	—3	+2
6	38	None	180	260	128	195	184	+32	+90 (O_2 leak in apparatus)

*ASA—acetylsalicylic acid.

Encouraged by the results of the controlled short-term study, aspirin has been employed in our diabetic outpatient department so that we could evaluate its long-term possibilities. It is as yet too early to report on this aspect in detail; however, our preliminary results suggest that this agent is effective on a long-term basis. We have had three previously difficult to control diabetics on a 6 gm. daily aspirin regimen as long as eight months with subjective (sense of well-being) and objective (normoglycemia) evidence of good control.

The mechanism of the blood sugar lowering action of salicylates is not known. Suggested actions include inhibition of gluconeogenesis, increased deposition of muscle glycogen, and increased conversion of glucose to fat.[3] Reid and McDougal[5] suggested an increased peripheral metabolism as a mechanism for the acetylsalicylic acid action because they were able to demonstrate a significant rise in the BMR in all seven of their patients during the aspirin treatment period. This is not confirmed in this study inasmuch as the BMR rose in only three patients and decreased in the other three during the period of treatment; there was no correlation of the changes in BMR with the effects on carbohydrate metabolism. There are many questions that must be answered before we can add aspirin to our already growing armamentarium of oral hypoglycemic agents that are used widely in clinical practice. However, as basic work continues in efforts to elucidate the true nature of the mechanisms of action, we may be approaching the goal of an ideal oral hypoglycemic agent, namely, one that parallels insulin in its metabolic effects, is inexpensive, readily available, and free of toxicity and significant side effects.

SUMMARY

Aspirin was used as a hypoglycemic agent in the treatment of six diabetic patients. In all six cases there was a marked drop in blood sugar during the period of treatment with aspirin. In all cases the blood sugar promptly returned to hyperglycemic levels after discontinuing the aspirin and substituting a placebo. Aspirin demonstrated effectiveness in long-term outpatient use. Suggested mechanisms of action are discussed.

SUMMARIO IN INTERLINGUA

Le Influentia de Salicylato Super Hyperglycemia

Aspirina esseva usate como agente hypoglycemic in le tractamento de sex patientes diabetic. In omne iste casos il occurreva un marcate reduction del sucro de sanguine durante le periodo del tractamento con aspirina. In omne le casos le sucro de sanguine retornava promptemente a nivellos hyperglycemic post le suspension del aspirina e le substitution de un placebo. Aspirina se monstrava efficace in le tractamento a longe vista de patientes visitante. Es discutite le possibile mechanismos del action.

ACKNOWLEDGMENT

I wish to acknowledge the aid of Drs. Karl E. Paschkis and Joseph J. Rupp in carrying out the above study.

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The Effect of Some Stressors on Steroid Diabetes in the Rat

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The author has reported[1] that the glycosuria of rats having steroid diabetes is suppressed by the presence of Walker carcinoma 256. Glycosuria is suppressed to a lesser extent by excision of skin. This report identifies two more stressors that suppress the glycosuria caused by hypercorticalism.

METHODS

Male rats (280-320 mg.) of the Sprague-Dawley strain were housed in individual metabolism cages and adapted to a tube-fed medium carbohydrate diet[2] in amounts of 13 ml. each morning and afternoon. Cortisone acetate was given by subcutaneous injection after each morning feeding in amounts sufficient to produce steroid diabetes. All rats received penicillin (5,000 units) and streptomycin (5 mg.) daily. Twenty-four-hour samples of urine collected each morning were analyzed for sugar by the method of Benedict.[3] Walker tumor 256 was injected as sterile undiluted homogenate (0.05 ml.) into the upper thigh of each hind leg. At the end of the experiment the tumor was dissected free from the muscle and weighed.

Neuromuscular stress was produced by securing the hind and fore legs to parallel bars on each side of the animal, who lay thus immobilized in an individual cage. Each leg was held fast by a band of adhesive tape which was easily applied and removed. Care was used to avoid tissue injury and signs of pain. All animals showed initial excitement and struggled to free themselves. Other rats were stressed by the injection of 0.5 ml. of 1.5 per cent formaldehyde solution each morning and late afternoon.

RESULTS

In Experiment 1 (figure 1), of thirty rats given 10 mg. each of cortisone acetate daily for ten days, seventeen rats were stressed with formaldehyde, and the rest served as controls. Glycosuria of stressed animals was markedly suppressed below that of the controls.

In Experiment 2 (figure 2), of twenty rats given 12.5 mg. each of cortisone acetate daily for ten days, eleven rats were stressed by immobilization, and the rest served as controls. The stressed animals again showed a marked suppression of glycosuria. In the immobilized rats the curve showing suppression of glycosuria rose characteristically and fell off from the peak by the ninth or tenth day. This suggests an adaptation period in which the stress is reduced in severity followed by an exhaustion of the capacity to adapt, the animals being very weak at nine or ten days.

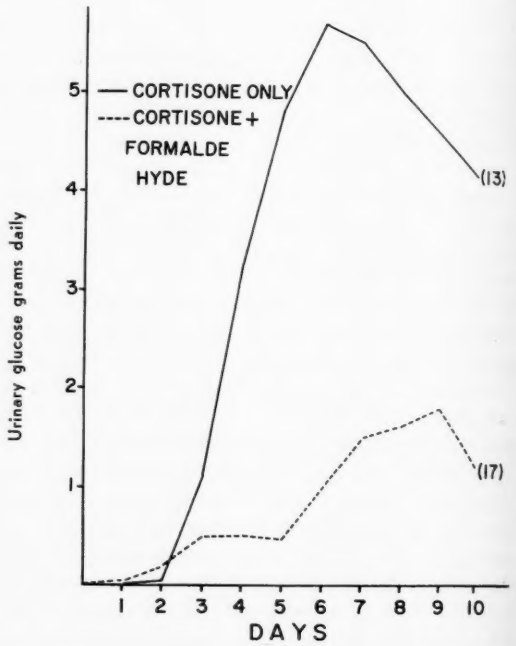

FIG. 1. Suppression of glycosuria by injection of 0.5 ml. of 1.5 per cent formaldehyde per rat per day. Each received 10 mg. daily of cortisone acetate.

In Experiment 3 (figure 3), of forty-one rats given 12.5 mg. each of cortisone acetate for ten days, eight were host to tumor, ten were subjected to immobilization, eleven received tumor and restriction together, and the twelve remaining animals served as controls. Tumor and restriction produced their characteristic

From The Ben May Laboratory for Cancer Research, The University of Chicago, Chicago, Illinois.

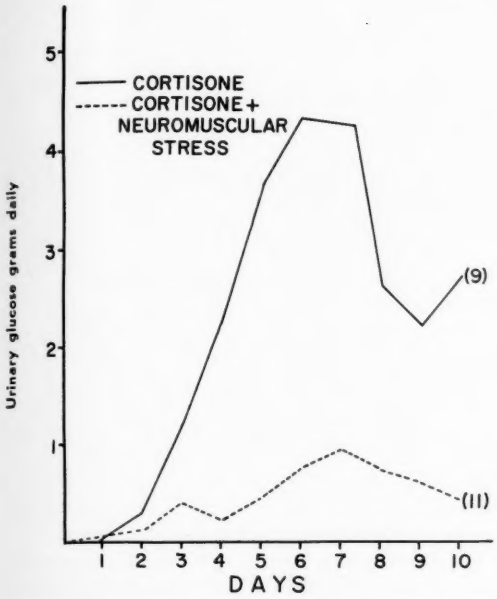

FIG. 2. Suppression of glycosuria by neuromuscular stress in rats; each received 12.5 mg. daily of cortisone acetate.

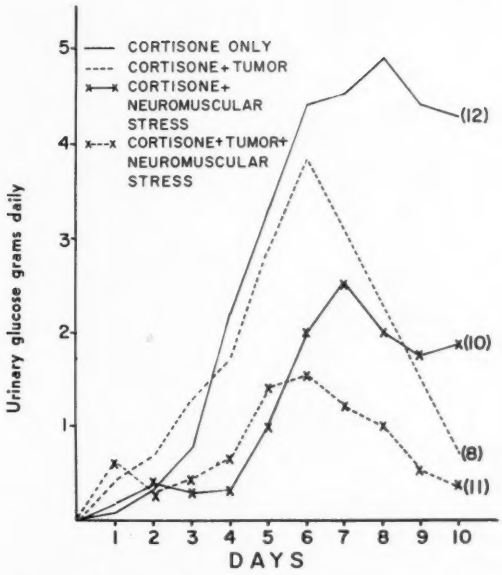

FIG. 3. Suppression of glycosuria by stressors in rats having steroid diabetes induced by 12.5 mg. of cortisone acetate per rat per day.

patterns of suppression, but glycosuria was lowest in the group subjected to the combined stressors.

DISCUSSION

It is clear that several stressors have a suppressive effect upon cortisone-induced glycosuria. It is not known that these stressors achieve their suppressive effects by the same mechanism. However, as a general property, stress seems to increase the needs of laboratory animals and patients for glucocorticoids, and to elicit this increase through hypophyseal release of corticotropin. The increased secretion of glucocorticoids during severe stress does not cause hypercorticalism but serves to meet an increased need for these hormones and to support homeostasis. We are interested in the proposition that a state of hypercorticalism induced under nonstress conditions might be alleviated by exposure to severe stress. Glycosuria is a secondary manifestation of hypercorticalism. We do not know of other symptoms of hypercorticalism that are suppressed by exposure to stress, but we are testing the possibility that other examples can be found.

SUMMARY

Several stressors were found to suppress the glycosuria caused by large doses of cortisone in the force-fed rat. These include Walker tumor 256, neuromuscular stress, surgery, and injection of dilute solutions of formaldehyde.

SUMMARIO IN INTERLINGUA

Le Effecto de Certe Stressores Super Diabete Steroidic in le Ratto

Esseva trovate que plure stressores supprime le glycosuria causate per grande doses de cortisona in le ratto sub alimentation fortiate. Istos include tumor 256 de Walker, stress neuromuscular, intervention chirurgic, e le injection de diluite solutiones de formaldehydo.

ACKNOWLEDGMENT

This research was supported by USPH Grant A-1653 and by a grant from Eli Lilly and Company.

The cortisone acetate, streptomycin and penicillin were kindly supplied by Dr. Robert O. Stafford, The Upjohn Company, Kalamazoo, Michigan.

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Effects of Experimental Diabetes on the Offspring of the Rat

Fetal Growth, Birth Weight, Gestation Period and Fetal Mortality

Jae Nam Kim, M.D., Ph.D., Walter Runge, M.D., Lemen J. Wells, Ph.D., and Arnold Lazarow, M.D., Ph.D., Minneapolis

It has long been recognized that pregnancy in women with diabetes mellitus is associated with a high fetal mortality and with a tendency to fetal gigantism.[1-3] In the attempts to produce similar complications in experimental animals, some workers have not observed increased birth weight or an increased frequency of overweight newborns in diabetes.[4,5] Others have claimed that giant newborn rats were obtained from pancreatectomized rats[6] and from rats with mild alloxan diabetes.[7] The reported effects of experimental diabetes on fetal mortality have varied widely from author to author.[6,8-10]

In the work presented here, diabetes was induced both before and after conception (on day 12), by pancreatectomy or by alloxanization. We have found that diabetes retarded the growth of fetuses and prolonged the gestation period. Because of this prolongation of the gestation period, the birth weight at spontaneous delivery usually approximated that found in normal controls. In a group of two rats in which there was the greatest prolongation of gestation, diabetes resulted in an increased birth weight which was largely attributable to the prolonged gestation. Experimental diabetes was usually associated with a significant increase in fetal mortality.

METHODS

The animals used in this study were a subline of the Sprague-Dawley strain (Holtzman). Most of them were virgin females whose ages varied between 120 and 150 days and whose weight ranged between 230 and 280 gm. The rats were fed a diet of Purina fox chow. Both food and water were supplied ad libitum.

Animals were injected with single doses of alloxan intravenously, via tail vein, 40 mg./kg. body weight, by the method of Lazarow and Palay.[11] Subtotal pancreatectomy was performed after the animals had been anesthetized with ether. After pancreatectomy the animals were given subcutaneous injections of 20 per cent glucose for a period of four days. Thereafter, they were force fed by stomach tube for six to ten days; this food was a diet* to which 3.46 gm. of pancreatin per 250 ml. of diet was added. Finally, the force feeding was stopped, and the animals were permitted to eat Purina fox chow.

Blood sugar levels and, in some cases, twenty-four-hour urinary glucose excretions were determined two to three times per week during the course of the experiment. The blood sugar was determined by the micro method of Folin-Malmros.[12] The urine sugar was determined by the caramelization method of Somogyi.[13]

A vaginal smear was made daily in each of the diabetic females, and those animals showing estrus were placed with males of the same strain and watched until copulation took place. The time was recorded, and the mated females were caged separately.

Unfortunately relatively few of the untreated diabetic rats carried their litters to term, and therefore the numbers of animals in some of the groups were necessarily small. When diabetes was induced prior to mating, the animals showed a decreased fertility and it was difficult to induce pregnancy. Of the diabetic rats that became pregnant, few carried their litters to term and a number of the pregnant diabetic rats died. When diabetes was induced on the twelfth day of pregnancy there was an increased maternal mortality; this was especially true of the pancreatectomized rats.

In subsequent studies alloxan was injected prior to mating and treatment of the diabetes was instituted within a few days after the alloxan administration.

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*High Carbohydrate Diet (Ingle, D. J., et al. Endocrinol. 39:52, 1946); or Medium Carbohydrate Diet (Ingle, D. J., and Meeks, R. C. Am. J. Physiol. 171:600, 1952).

Protamine Zinc Insulin was given in doses of five or ten units per kilogram per day and the insulin treatment was continued during the period the animals were mated and subsequently during pregnancy. Later when the pregnancy was well established severe diabetes was induced in some animals by withdrawing insulin. In one series of twenty-seven diabetic pregnant rats, the insulin was stopped on the twelfth day of pregnancy (suddenly, twenty cases; gradually from day ten to day twelve, seven cases), with the hope that the pregnancies would continue. However, even in this instance only six pregnancies were carried successfully to term (Group 4).

Beginning at twenty-one days and fifteen hours postcoitum, i.e., one hour prior to the earliest time of delivery in normal pregnancies (Wells),[34] the rats were closely watched at fifteen- to thirty-minute intervals. Spontaneous deliveries were witnessed, in order to make accurate observations on the length of the gestation period, on the number of stillborns and liveborns, and on litter size.

Fetuses or newborns were weighed individually immediately after severance of the umbilical cords or after parturition and before they had nursed. Stillborns were likewise weighed and included in the average unless they showed signs of necrosis. In weighing, the chainomatic balance was read to the closest milligram.

RESULTS

Table 1 shows the experimental groups used and their characterization, i.e., the method of inducing diabetes, duration of diabetes, duration of insulin treatment and the time at which the observations on weight and mortality were made. Table 2 shows the characteristics of the diabetes in the various groups of pregnant rats.

1. *Maternal diabetes and growth of fetuses in utero*: Pregnancy was interrupted at a standard period of gestation, that is, 519 hours postcoitum or twenty-one days and fifteen hours after witnessed mating. Body weights of fetuses at 519 hours (519-hr. weight) in normal and diabetic mothers of various groups (Groups 8 through 13) are shown in figure 1. In this instance the average weight of the entire litter was used to calculate the standard deviations and statistical significance.* The 519-hr. weight in each of these diabetic groups was compared with that of the normal controls (Group 8). A statistically significant decrease in the 519-hr. weight (ranging from 13.4 to 43.8 per cent) was invariably observed in all the diabetic groups. The diabetic groups studied included animals that were made diabetic on the twelfth day of gestation by alloxan injection (Group 11), and by pancreatectomy (Group 13).

When the diabetes was induced prior to pregnancy by either alloxan injection (Group 9) or pancreatectomy (Group 12) the 519-hr. fetal weights were lower than was the case when the diabetes was induced on day 12 (Groups 11, 13). Of thirty-three female rats which were pancreatectomized before attempted matings, only one survived and yielded fetuses at 419 hours postcoitum (Group 12). Although figure 1 does not

*For assistance in the statistical consideration of the data, the authors are indebted to Dr. Eugene A. Johnson, Department of Biostatistics.

TABLE 1
Characterization of the various groups of animals

Groups	Litters	Method of producing diabetes	Duration of diabetes	Insulin treatment	Time of observation
1	39 Normal	O	0	0	Birth
2	2 Diabetic	A	Entire preg.	0	"
3	16 Diabetic	A	" "	Entire preg.	"
4	6 Diabetic	A	" "	0-12 da	"
5	11 Diabetic	A	12 da-term	0	"
6*	17 Normal	O	0	0	"
7*	10 Diabetic	A	12 da-term	0	"
8	28 Normal	O	0	0	519 h. pc.
9	2 Diabetic	A	Entire period	0	"
10	2 Diabetic	A	" "	Entire period	"
11	15 Diabetic	A	12 da-term	0	"
12	1 Diabetic	P	Entire period	0	"
13	4 Diabetic	P	12 da-term	0	"
14	14 Diabetic	A	12 da-autopsy	0	17-21 days
15	23 Normal	O	0	0	"

A, Alloxan injection.
P, Subtotal pancreatectomy.
h. pc., hours postcoitum.
*Rats operated at 519 hr. postcoitum, and two or three fetuses removed. Subsequently, the rats delivered remaining fetuses spontaneously.

TABLE 2

Severity of diabetes in various groups of pregnant rats during the course of the pregnancies

	Groups	No. animals	Range of average daily urine sugar excretion (gm.)	Range of average blood sugar (mg. per 100 ml.)	Range of average dose of insulin (units/kg.)
2	Diab., 0-term	2	5.08-5.10	356-363	0
4	Diab., 0-term; ins., 0-12 da	6	1.10-3.26* 2.68-4.94†	233-404* 291-387†	9-10* 0†
5	Diab., 12 da-term	11		291-458	0
7	Diab., 12 da-term	10		301-470	0
		4	less than 1	149-186	4.3-9
3	Diab., 0-term; ins., 0-term	7	1-2	197-281	4.3-10
		5	more than 2	303-384	9-10

*During insulin treatment.
†After insulin treatment was discontinued.

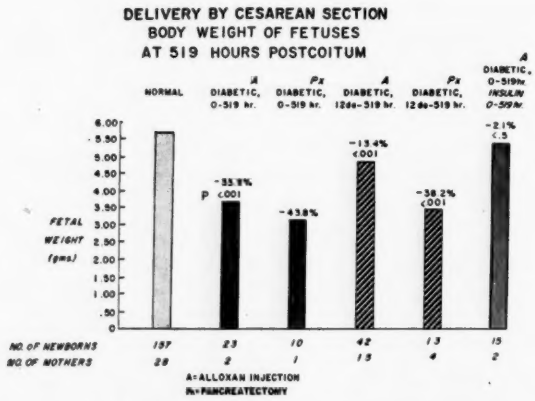

FIG. 1. From left to right the bars show the data on Groups 8, 9, 12, 11, 13 and 10, respectively (table 1). The average per cent change in weight at 519 hours, and the p values, compared to the normal, are also shown.

show a p value for group 12, the differences between the means of the experimental and control fetal weights was thirty-four times the standard error of the control group (Groups 12 and 8, respectively). By contrast when the diabetes was treated with insulin, retardation of fetal growth was not observed; in Group 10 where diabetes was produced prior to pregnancy and where insulin treatment was continued throughout pregnancy, the 519-hr. weight was almost the same as that in the normal controls.

An effort was made to determine how early the retardation of fetal growth could be detected. Diabetes was induced by alloxan injection on day 12 and fetuses were removed at various stages of pregnancy, between day 17 and 21 (groups 14, 15). The data are summarized in figure 2. Statistically significant decreases in fetal weights were observed at twenty and twenty-one days of gestation. Although not statistically significant, the fetal weights in the diabetic group also tended to be smaller than the control weight on days 17 to 19.

2. *The effects of diabetes on the length of gestation, birth weight, litter size and fetal mortality*

Length of gestation period: All the animals were allowed to deliver their young spontaneously. The diabetic groups included: (a) two mothers that were made diabetic before conception by alloxan injection and that received no insulin (Group 2); (b) eleven untreated rats that were made diabetic on the twelfth day of gestation by alloxan injection (Group 5); six rats that were made diabetic by alloxanization before pregnancy and that then received insulin only up to day 12 (Group 4); and (d) sixteen treated rats that were made diabetic before conception and that received insulin throughout the pregnancy (Group 3).

The severity of the diabetes in each group, as judged

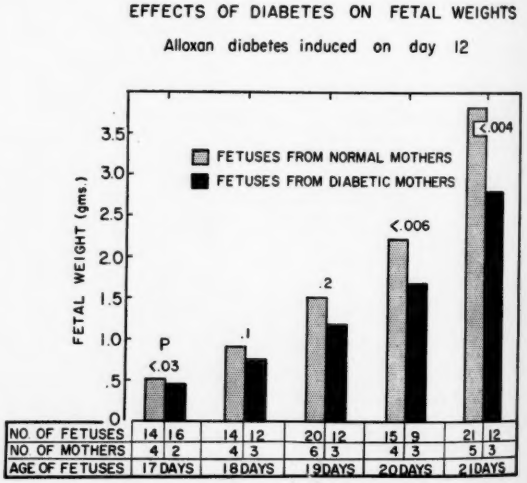
EFFECTS OF DIABETES ON FETAL WEIGHTS
Alloxan diabetes induced on day 12
FETUSES FROM NORMAL MOTHERS
FETUSES FROM DIABETIC MOTHERS
FETAL WEIGHT (gms.)
P <.03
.1
.2
<.006
<.004
NO OF FETUSES 14 16 14 12 20 12 15 9 21 12
NO OF MOTHERS 4 2 4 3 6 3 4 3 5 3
AGE OF FETUSES 17 DAYS 18 DAYS 19 DAYS 20 DAYS 21 DAYS

FIG. 2. In each pair of bars, the left bar represents Group 15 and the right Group 14.

by the blood sugar and the urine glucose excretion, is shown in table 2.

Figure 3 shows that the gestation period was significantly prolonged in all of the diabetic groups except those that were treated with insulin throughout pregnancy. In this latter group, the length of the gestation period was the same as that in the normal controls.

Birth weight and litter size: A significant increase in the average birth weight was observed in the untreated group in which the mothers were diabetic throughout pregnancy (Group 2), but unfortunately only two of this group carried their litters to term; one rat (2854) had a litter of three newborns in which the average birth weight was 8.280 gm., the second (2864) had a litter of ten in which the average birth weight was 7.232 gm.

In the group in which diabetes was induced by alloxan injection on the twelfth day of pregnancy the average birth weight did not differ significantly from the normal (+2.8 per cent).

A significant decrease (13.7 per cent) in the average birth weight was observed in the diabetic group in which the mothers were injected with alloxan prior to conception and in which insulin had been injected daily from day 0 to day 12 and then withheld after the twelfth day (Group 4). In this group, the mothers had hyperglycemia and glycosuria throughout pregnancy, despite the injection of insulin from day 0 to day 12 (table 2).

In order to study the frequency of overweight newborns, the distribution of birth weights within the litters was analyzed. The birth weight of individual newborns was used to calculate the standard deviations. The mean birth weight in 289 newborns from normal mothers was 6.274 gm. One standard deviation of the mean

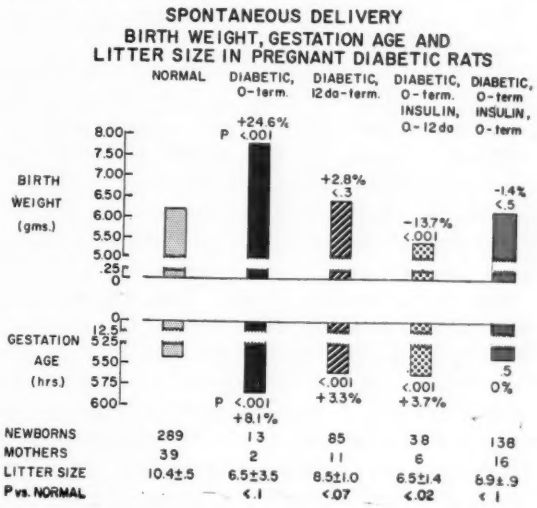

FIG. 3. From left to right, the bars show the data on Groups 1, 2, 5, 4 and 3, respectively (table 1). The per cent change in birth weight, the per cent change in the length of gestation period, and the p values, compared to the controls, also are shown.

was 0.555 gm. Table 3 shows the percentages of newborns whose weights exceeded the mean birth weight of the normal controls by one, two and three standard deviations respectively. In all of the experimental groups (except Group 4) there was a higher incidence of newborns whose weights were greater than 7.384 gm., i.e., two standard deviations greater than the average in the control group.

The average litter size of the various groups is shown in figure 3. In general the litter size did not differ markedly from the control group with the exception of Group 4 (diabetic, 0-term; insulin, 0-12 day) in

TABLE 3
Incidence of overweight newborns from diabetic mothers

Number of standard deviations greater than average normal birth weight*	Birth weight in grams	Number of animals and incidence per cent	Groups 1 Normal	2 Diabetic, 0-term	3 Diabetic, 0-term; insulin, 0-term	4 Diabetic, 0-term; insulin, 0-12 da	5 Diabetic, 12 da-term
1	6.829 or more	number	41	10	23	6	14
		per cent	14.2	76.9	16.7	15.8	16.5
2	7.384 or more	number	3	7	5	0	6
		per cent	1.0	53.8	3.6	0	7.1
3	7.939 or more	number	0	3	1	0	1
		per cent	0	23.1	0.7	0	1.2
Total number of newborns			289	13	138	38	85

*The average normal birth weight was 6.274 gm.
One standard deviation of the normal birth weight was ± .555 gm.

which a significant decrease in the litter size was observed (p less than 0.02).

Fetal mortality: The fetal mortalities for the various groups of animals are shown in figure 4. Most of the dead animals were stillborns; those newborns which had reflexes but which failed to breathe and survive are also included in the mortality figures. In all diabetic groups, the fetal mortality rate was significantly higher than that in normal controls. The highest mortality rate (47.6 per cent) was observed in Group 4 (diabetic, 0-term; insulin 0-12 day). This rate was about eight times higher than that of controls (5.9 per cent).

3. *The effects of removing two to three fetuses upon subsequent birth weight at spontaneous delivery*: Included in this study were Groups 6 (normal, laparotomy) and 7 (diabetic day 12 to term, laparotomy). From each gravid rat, two to three fetuses were removed by cesarean section at 519 hours (twenty-one days and fifteen hours) postcoitum; they are included in Groups 8 and 11, table 1. Thereafter, the animals were allowed to deliver the rest of the fetuses spontaneously. Table 4 shows that the fetal weight at 519 hours of gestation was significantly lower in the diabetic group

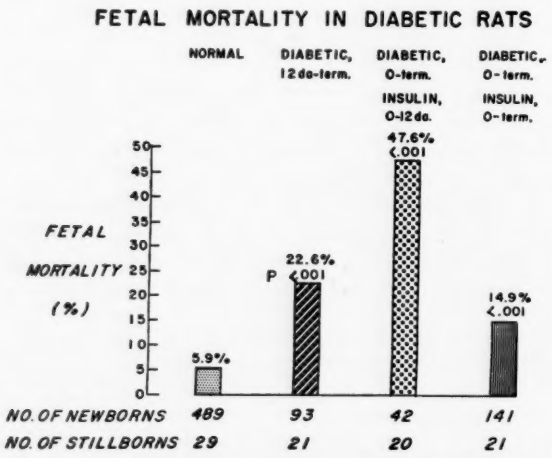

FIG. 4. From left to right, the individual bars show data from Groups 1, 5, 4 and 3, respectively (table 1). The p values were determined by the Chi Square method.

than in the control. At the time of spontaneous delivery, the birth weights in the two groups were not significantly different. The gestation period in the diabetic group was fifteen hours longer than that in the normal group. It is reasonable to suppose that during the extra fifteen hours of intrauterine life the fetuses continued to grow and that because of this the birth weight approximated that of normal controls which were delivered fifteen hours earlier. The surgical intervention shortened the length of the gestation period by five hours in normal rats and by eight hours in diabetic rats. If they had not been operated, they should have delivered their young at 542 hours (Group 1, normal) and 560 hours (Group 5, diabetic, day 12 to term), respectively. In normal rats the operation shortened the gestation period 0.92 per cent; in diabetic rats it decreased the gestation period 1.43 per cent.

4. *Relationship among birth weight, gestation period and litter size*

Correlation between birth weight and gestation are: In the normal group, a positive correlation was observed between the birth weight and gestation age; the correlation coefficient was: $r = 0.58$. The slope of the dashed regression line in Figure 5 was determined: birth weight in grams $= -3.489 + 0.018146x$, where x is the gestation age in hours.

In a diabetic group (Group 5, diabetic, day 12 to term), there was likewise a positive correlation between the birth weight and gestation age. The slope for the solid regression line in figure 5 was determined: birth weight in grams $= -8.3849 + 0.0264x$, where x is the gestation age in hours.

From the two regression lines in figure 5, the predicted weights at gestation ages of 519, 542 and 560 hours were obtained (table 5). All the predicted weights fell within the range of 1.5 standard deviations from the means of the actual weights.

Relation of birth weight to litter size: When the average birth weights in thirty-seven litters from normal mothers were plotted against the litter sizes, there was no correlation between these two variables (Kim's figure 4).[15] Therefore, litter size was not taken into account in analyzing the birth weights in the experimental groups.

Relation of gestation period to litter size. When the gestation periods and litter sizes in thirty-eight litters from normal mothers were studied, no correlation between these variables was noted (Kim's figure 5).[15]

DISCUSSION

By witnessing both mating and parturition it was possible to minimize the error in determining the length of the gestation period. It has been reported that ovulation in the rat occurs about seven to eleven hours after the beginning of estrus (Blandau and Soderwall).[16] We have found that our normal and diabetic rats showed a wide range in the time of appear-

TABLE 4

Effects of removing two or three fetuses upon the subsequent birth weight at spontaneous delivery*

	At 519 hours postcoitum				At spontaneous delivery					
			Fetal weight				Birth weight		Gestation age	
Mothers	Groups	No. of litters	Mean & S.E. (gm.)	P	Groups	No. of litters	Mean & S.E. (gm.)	P	Mean & S.E. (hr.)	P
Normal controls	5	28	5.52±.07		6	17	6.131±.101		537±2.4	
Diabetic, 12 da-term	8	15	4.78±.20	<.001	7	10	5.836±.127	.1	552±4.2	<.07

*From each gravid rat, two or three fetuses were removed by cesarean section at 519 hours postcoitum. Subsequently, the mother delivered the remaining fetuses spontaneously.

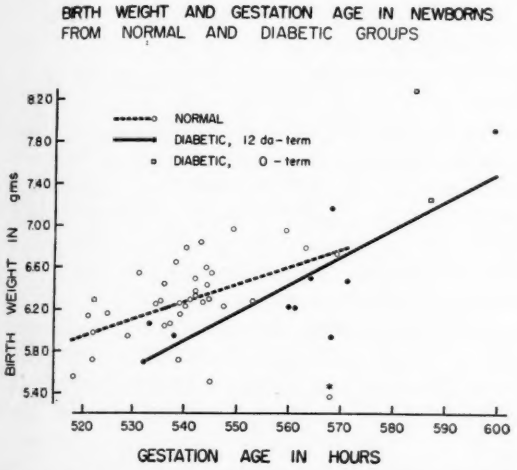

FIG. 5. Scattergraph of data from Groups 1 (open circles), 5 (black dots) and 2 (squares). The solid line is the regression line for Group 5. The dashed line is the regression line for the normal Group 1: In calculating it, the litter marked by the star was omitted because this litter seemed to be abnormal; the mother actually failed to deliver one of the fetuses (tenth of the litter).

ance of estrus; this varied from 10 p.m. to 4 a.m. The witnessing of parturition also minimized the error in determining the body weight and fetal and/or neonatal mortality: The exact time of parturition was known; the birth weight was obtained before the young had any milk in the stomach; the mother was prevented from destroying any member of her litter.

Our data showed that diabetes in the absence of insulin treatment retarded the growth of fetuses by 13.4 to 43.8 per cent. This was true regardless of whether the diabetes was produced by alloxan injection or by pancreatectomy or whether it was induced on day 12 or prior to conception. This retardation was observed on the twentieth, twenty-first and twenty-second days of gestation. When the diabetes was treated by daily insulin injections, (up to 519 hours postcoitum), the retardation of growth was not observed.

TABLE 5

Comparison of predicted and actual values of 519-hour weights and birth weights*

Gestation age, hours postcoitum	Weights	Mean weights & S.D. (gm.) Normal, Groups 8 & 1	Diabetic, 12 da-term, Groups 11 & 5
519	Predicted	5.93	5.33
	Actual	5.52±.37	4.77±.75
542	Predicted	6.34	5.94
	Actual	6.22±.51	
560	Predicted	6.59	6.42
	Actual		6.40±.65

*Predicted weights are based on the regression lines in figure 5.

Although many other workers have studied pregnancy and experimental diabetes, we are not aware of any published record of the weights of fetuses from diabetic mothers at a standardized period of gestation.

Our results also showed that diabetes in the absence of insulin treatment prolongs the gestation period. Insulin treatment prevented this prolongation if it was given daily throughout the pregnancy.

Because of the prolongation of the gestation period in the diabetic rats, the birth weights at spontaneous deliveries were more variable. In our Group 5 (diabetic, day 12-term), the average birth weight at spontaneous delivery was slightly greater (2.8 per cent) than that in Group 1 (normal) whereas at 519 hours it was 13.4 per cent less than that of the control. Thus the extra eighteen hours of prenatal life allowed the fetuses extra time for growth in utero (figure 6). In our Group 2 (diabetic 0-term), the average birth weight was considerably greater (24.6 per cent) than that in Group 1 (normal) whereas at 519 hours it was 33.9 per cent less than that of the control. Thus the extra forty-four hours of prenatal life allowed still more time for growth in utero and permitted the diabetic birth weight to exceed that of the normal. Although the difference between the two means was statistically significant (p less than 0.001), Group 2 consisted of only

two litters because very few of the untreated diabetic rats in this group carried their litters to term.

Insulin treatment of the diabetes throughout pregnancy prevented both the retardation of fetal growth and the prolongation of the gestation period and consequently there was no change in the spontaneous birth weight (figure 3, Group 3: diabetic, 0-term; insulin, 0-term).

When the insulin treatment was stopped on the twelfth day postcoitum (Group 4: diabetic, 0-term; insulin, 0-day 12; figure 3), the weight at spontaneous birth was significantly reduced (13.7 per cent) even though there was a significant prolongation of gestation period. In comparing this group in which insulin treatment was stopped on day 12 with Group 5 (diabetic, day 12-term), where the diabetes was induced on day 12 it should be noted that the gestation periods were prolonged equally in both. However, a reduction in spontaneous birth weight was observed in Group 4 where the diabetes was present throughout pregnancy and twice as long as that in Group 5.

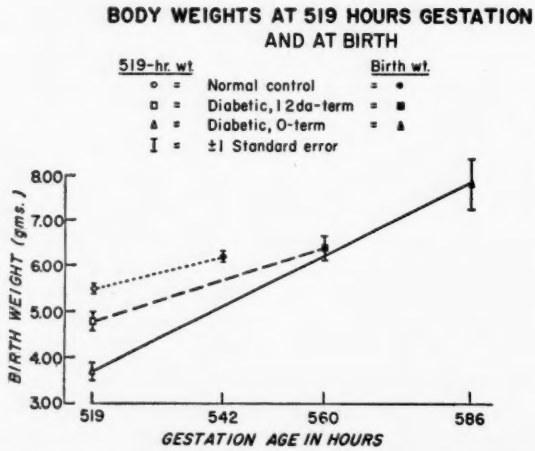

FIG. 6. Data on 519-hour weight: Group 8, open circle; Group 11, open square; Group 12, open triangle. Data on spontaneous birth weight: Group 1, black circle; Group 5, black square; Group 2, black triangle.

The fetal mortality in Group 4, i.e., the group in which insulin treatment was withdrawn on day 12, was the highest observed in our series (47.6 per cent); the stillborns tended to be smaller than the liveborns. In four of the six litters of this group, there were three to five stillborns per litter; the maximal weight of these stillborns was 0.584 gm. smaller than the average birth weight of the normal controls.

The highest incidence of overweight newborns, i.e., newborns whose weights were more than two standard deviations greater than the mean weight of normal controls, was observed in Group 2 (diabetic, 0-term). Of the two litters in this group one litter had three newborns, all overweight; the second litter with ten newborns had four overweight animals. Higher than normal incidences of overweight newborns were also observed in two other diabetic groups of animals even though the over-all average birth weights for these two groups were almost normal. In Groups 3 (diabetic, 0-term; insulin, 0-term) and 5 (diabetic, day 12-term) the incidences of overweight newborns were 3.6 and 7.1 times higher, respectively, than that of the normal (1 per cent).

The fetal mortality in all of the experimental groups, shown in figure 4, was significantly greater than that in the control group. This observation suggests that the diabetes per se, or some complication of diabetes, is the causative factor. Ketone bodies are thought to cross the placental barrier[17] and they might be a contributing factor. The highest fetal mortality in the various diabetic groups was observed in Group 4 (diabetes, 0-term; insulin 0-day 12), i.e., the group in which insulin treatment was stopped on day 12; this might be a consequence of the markedly altered metabolic disturbance due to the cessation of insulin treatment. Fetal mortality was not analyzed in Groups 2, 6 and 7 (table 1).

The results which we have obtained help to clarify the apparently contradictory results which have been reported by previous workers. For example, several workers who injected alloxan into animals either before or after conception reported no increase in the birth weight and/or gestation period.[4,5,9,10]

On the other hand, Hultquist[6,18] reported an increased birth weight in two out of seven groups of untreated pancreatectomized diabetic rats and in two out of nine groups of diabetic rats treated with 3 to 12 units of insulin per kilogram per day. It should be noted, however, that Hultquist's data indicated that five out of seven groups of untreated diabetic rats and six out of nine groups of diabetic rats treated with insulin showed significant decreases in their birth weights. He concluded that the insulin treatment did not influence the birth weight or the gestation period. His nine groups of pancreatectomized rats which were treated with insulin are somewhat comparable to our Group 3 (diabetic, 0-term; insulin, 0-term) in which the insulin treatment prevented both the increase in birth weight and the prolongation of the gestation period. Hultquist's data are more difficult to interpret because the length of the

gestation periods was not as accurately timed as in the present work. He did not state that he witnessed all deliveries and hence one cannot be sure that the body weights were obtained before the young had suckled milk and before postnatal dehydration had occurred. Hultquist likewise determined his standard errors by taking the birth weights of individual newborns as an independent variable; this did not consider the fact that the variability between litters is usually greater than that within a litter.

Solomon[7] has reported an increased birth weight in newborns from diabetic rats given alloxan during pregnancy, and, in one diabetic group, he stated that an increased birth weight was observed in rats with normal gestation periods. Since the fetal weight increases very rapidly during the terminal hours of pregnancy, i.e., from 5.52 gm. at 519 hours postcoitum to 6.22 gm. at 542 hours, or an increase of 0.7 gm. in twenty-three hours, a slight error of only a few hours in the estimated length of gestation would result in a large difference in the birth weights obtained. Thus, since Solomon did not specifically state that he witnessed both mating and delivery in every rat of his series, the reported length of the gestation period might not be sufficiently accurate to justify his conclusion.

Although the mechanism by which diabetes prolonged the gestation period is not understood, this may be related to changes in chorionic gonadotrophin levels. White and her associates[23] have reported that the serum chorionic gonadotrophin levels tended to be increased in diabetic women. When extracts of urine from pregnant women were injected into pregnant animals, including rats, the pregnancy was prolonged and the fetuses were enlarged.[19,21] Similarly, the injection of chorionic gonadotrophin into pregnant rats prolonged the gestation period and increased the birth weight.[22]

Our observations are regarded as conclusive evidence against any notion that experimental diabetes speeds up the growth of fetuses. Instead, it retards the growth of them. We are extending the study for the purpose of determining the causative factor or factors.*

SUMMARY AND CONCLUSIONS

Diabetes was induced by alloxan injection or by pancreatectomy either before conception or on the twelfth day of gestation. Most of the groups of diabetic rats were untreated. In those rats that were treated with insulin, the doses of insulin administered were not large enough to control the hyperglycemia and the glycosuria. In one group, insulin treatment was given during the first twelve days of gestation and then stopped.

There is a positive correlation between the birth weight and the length of the gestation period for both the normal and diabetic pregnant rats.

Diabetes, regardless of the method of inducing it, retards the growth of fetuses, as indicated by decreased fetal weights at 519 hours postcoitum.

Diabetes prolongs the length of the gestation period and, consequently, the average weight at spontaneous birth approaches that of the control. It may even exceed that of the normal; this was observed in the two rats that had the greatest prolongation of gestation.

The frequency of overweight newborns, i.e., weights exceeding the average normal weight by two or more standard deviations at spontaneous delivery, is usually higher in untreated diabetic rats than in normal. This was observed even though the average birth weight in the diabetic group is not significantly different from that of the normal.

Pregnancies in diabetic rats are usually associated with a high fetal mortality.

Insulin treatment throughout pregnancy prevents both the prolongation of gestation and the retardation of fetal growth. Although insulin treatment reduces the fetal mortality, the observed mortality in the treated group is still greater than that of the normal.

The removal of two or three fetuses of a litter by cesarean section at twenty-one days and fifteen hours postcoitum (519 hours) seems to hasten the spontaneous delivery of remaining fetuses both in diabetic and in normal rats.

SUMMARIO IN INTERLINGUA

Le Effectos de Diabete Experimental Super le Prole del Ratto: Le Crescentia Fetal, le Peso Natal, le Periodo Gestatori, e le Mortalitate Fetal

Diabete esseva inducite in rattas per injectiones de alloxano o per pancreatectomia (1) ante le conception o (2) le dece-secunde die de gestation. In le majoritate del casos, le diabete non esseva tractate. In le caso del rattas tractate con insulina, le dosage non sufficeva a dominar le hyperglycemia e le glycosuria. In un gruppo de rattas diabetic, insulina esseva administrate durante le prime dece-duo dies del gestation e suspendite subsequentemente.

Il existe un correlation positive inter le pesos natal e le duration del periodo gestatori tanto in rattas normal

*The present paper is one of our current series on diabetes and pregnancy in the rat.[24-26]

como etiam in rattas diabetic.

Diabete, sin reguardo a como illo es inducite, retarda le crescentia del fetos, a judicar per le observate reduction del peso fetal a 519 horas post le coito.

Diabete prolonga le gestation. Le peso medie del prole de rattas diabetic al tempore del nascentia spontanee approcha per consequente le peso natal in observationes de controlo. Illo mesmo pote exceder le valor normal. Isto esseva le caso in le duo rattas con le plus marcate prolongation del periodo gestatori.

Le frequentia de neonatos a peso excessive — i.e. pesos que excede le valor medie in casos normal per duo deviatones standard o plus al tempore del parturition spontanee — es usualmente plus alte in non-tractate rattas diabetic que in normales. Iste constatation non contradice le facto que le peso medie total del neonatos in le gruppo del matres diabetic non differe significativemente ab illo in normales.

Le pregnantia de rattas diabetic es usualmente associate con un alte mortalitate fetal.

Tractamento a insulina durante le pregnantia preveni le prolongation del periodo gestatori e etiam le retardo del crescentia fetal. Ben que insulina reduce le mortalitate fetal, le observate mortalitate in le gruppo tractate remane plus alte que in gruppos normal.

Le elimination de duo o tres fetos per section cesaree a 519 horas post coito pare accelerar le parturition pro le resto del portata tanto in rattas diabetic como etiam in rattas normal.

ACKNOWLEDGMENT

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Special Article

Teaching of Diabetes in Medical Schools

Proceedings of the Diabetes Program Directors' Workshop[1]

Arthur R. Colwell, Sr., M.D., Chicago, General Chairman

INTRODUCTION

This conference was concerned with methods of education, research and care of patients with diabetes in the medical schools in the United States. Its primary purpose was an interchange of useful information among educational institutions. Two principles guided its program: first, the tacit understanding that the earlier and more efficient the educational process, the better the product; and second, the idea that free communication among intelligent and interested people yields good dividends. Accordingly, the American Diabetes Association and the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health again joined forces to bring together national leaders in diabetes teaching, research and practice. Their immediate focus was teaching and training in American medical schools. Many zones of activity in diabetes revolve around the work of the schools, such as research, training of ancillary personnel, education of patients, development of future faculties, and postgraduate education of physicians. Therefore, discussions at the conference reached beyond the schools.

Attendance: Seventy-nine individuals from various parts of the country participated. They included fifty Program Directors of diabetes training grants from the National Institutes of Health, or their delegates, in forty-seven educational institutions; twenty members of the Council of the American Diabetes Association; and nine members of the Training Grants Committee and staff of the National Institute of Arthritis and Metabolic Diseases and U.S. Public Health Service. A list of participants and institutions represented is appended, together with names of committee and staff members responsible for the program and arrangements.

Opening Session. At the general meeting which opened the conference on Friday evening, January 22, participants were welcomed by Francis D. W. Lukens, M.D., President of the American Diabetes Association, and by Floyd S. Daft, Ph.D., Director of the National Institute of Arthritis and Metabolic Diseases. Policies, procedures and intended purposes of grants to assist training and research in diabetes were described by Ralph E. Knutti, M.D., Chief Extramural Programs Branch of the Institute. Fifty-nine organized training programs now exist in American universities, schools and hospitals. Particulars can be obtained by communicating with the Institute at Bethesda 14, Maryland.

The well-established program in diabetes at Harvard University Medical School of which George W. Thorn, M.D., is director was described in detail by Albert E. Renold, M.D. The following is a condensed version of his report.

The program is primarily oriented toward improving the value of existing research in diabetes and intermediary metabolism within two major teaching groups. The first group is the endocrine-metabolic unit which comprises four subdivisions: (1) the endocrine and steroid laboratory with two senior investigators and six research fellows; (2) the diabetes-intermediary metabolism unit with two senior investigators and six research fellows; (3) the thyroid unit with one senior investigator and one research fellow; and (4) the tissue electrolyte unit with one senior investigator and three research fellows. There is little difference between the activities of research fellows and trainees, except for some specific additional clinical duties for the trainees. The unit is responsible for a nine-bed metabolic ward, the endocrine-metabolic and diabetes clinics, and related teaching and consultations within the hospital. The second major group comprises students, house staff and research fellows in other specialties in active training at the Peter Bent Brigham Hospital.

[1] The Diabetes Program Directors' Workshop, held in the Ambassador Hotel, Los Angeles, Jan. 22-23, 1960, was sponsored jointly by the American Diabetes Association and the National Institute of Arthritis and Metabolic Diseases.

The teaching methods and objectives described in this report represent the combined thinking of participants in the Conference, chiefly those responsible for teaching of diabetes in American medical schools. These comprise most of the current Directors of Graduate Training Grants in the field of diabetes awarded by the National Institute of Arthritis and Metabolic Diseases as well as officials of the American Diabetes Association.

The ideas expressed do not necessarily reflect the policies and objectives of the Diabetes Graduate Training Grant program of the National Institute of Arthritis and Metabolic Diseases. A statement concerning these policies can be obtained from the Chief, Extramural Programs, National Institute of Arthritis and Metabolic Diseases, Bethesda 14, Maryland.

The training program attempts to fulfill its aims primarily by providing personnel with integrated research and training interests. In addition to the director, the nucleus of the program is made up of an independent investigator of junior faculty rank, two trainees, a full-time teaching nurse, a teaching dietitian, and a part-time teaching technician who is chief technician of the research laboratory. It is desirable that all of these individuals have *both* research and clinical training functions. While this is especially important for the independent investigator and the trainees, this aim also has been achieved with the teaching nurse, dietitian and technician. A training procedure used by the program makes available to the house staff more precise quantitative methods in the evaluation of clinical problems, such as helping in the performance and interpretation of rapid intravenous glucose tolerance tests with calculation of the glucose disappearance coefficient, or permitting the study of selected patients on the metabolic ward.

An important area of progress concerns continued efforts to improve the ability of the individuals involved to carry on simultaneously their two sets of responsibilities (research and training) without in any way decreasing the quality of their activities in either field. It is at this level that the training program sponsored by the Institute of Arthritis and Metabolic Diseases has been and is most helpful.

Robert H. Williams, M.D., director of another active training program at the University of Washington School of Medicine in Seattle, reported on current developments at this new school, including its training program in endocrinology and metabolism. The full report is to be published elsewhere. An abridged version follows:

Acquisition and understanding of available knowledge concerning diabetes, as with many other diseases, is a mammoth task. Optimal accomplishments require: (a) careful studies of the entire curriculum, with appropriate modifications; (b) a desirable number and type of patients; (c) sufficient staff with proved capacity to teach; and (d) adequate research opportunities for students and graduates.

The curriculum at the University of Washington has been evaluated thoroughly and our conclusions are that there must be increased effort (a) to define goals and make them known to faculty, students, and others; (b) to become acquainted with the work of other divisions and departments; and (c) to increase coordination in teaching. The amount of vertical teaching has been greatly increased. For example, there is increased collaboration in conjoint teaching by endocrinologists in basic science and clinical science departments. Training of students, residents, and research fellows in three teaching hospitals is carefully integrated. All of the work of the health sciences, including the University Hospital, is housed in one building, a physical arrangement which has promoted collaboration in teaching and research.

In view of the tremendous progress in medicine, we have attempted to stimulate initiative, originality, independence, and creativeness. We have encouraged the acquisition of new concepts and the testing of their validity. This has emphasized the importance of training in research. Therefore, we have offered formal courses dealing with general principles in research: philosophy, experimental design, biometrics, reading, writing papers, etc. We have also offered specific courses in methodology and in individual sciences. A good supply of research fellowships and encouragement from the faculty have helped induce about 100 students to spend summers in research, and 5 to 10 per cent to withdraw from their standard curriculum to spend a year or more in research. There are five graduate research fellows in endocrinology and metabolism. Six biochemists who are employed full time in the Department of Medicine have been of enormous aid in their training.

It is important that sufficient time be spent with individual trainees, dealing not only with their immediate scientific problems but also with their working conditions, philosophy, future goals, etc. Appropriate stimulation and orientation toward the best objectives often promote more progress than an eloquent dissertation on medical facts. Both are important.

Thaddeus S. Danowski, M.D., program director at the University of Pittsburgh School of Medicine and chairman of the Committee on Professional Education of the American Diabetes Association, presented a thoughtful paper entitled "Universities as the Internal Controls in Government Aid." In accordance with policy to report the proceedings of the conference only in summary form Dr. Danowski has condensed his paper into the following version:

In the tradition of free enterprise in which we have been raised it is logical to become concerned about the ever-increasing role of government funds in medical education. In university-sponsored medical areas many precautions have been taken to see that medical education remains in the hands of medical educators, i.e., in your hands and mine. I can best illustrate by reviewing the measures which assure that universities shall function as internal controls in government aid, and by expressing concern about policies in some universities which are unduly or potentially restrictive.

I know of no private enterprise, no matter how anxious to please, that grants the consumer the controlling role in the creation and distribution of its products. Yet this is actual government policy with respect to funds for teaching, research, and certain aspects of patient care. Any educator, scientist or clinician may submit a request for aid. The basic procedures are simple and familiar to all: Certain forms must be used, time deadlines must be met, applications must be sponsored by suitable institutions, the rights of the public to any findings must be protected, and an audit of disbursement of funds is necessary.

The process whereby applications are granted or denied begins with assignment to a particular Institute, Study Section and Council by full-time administrative personnel. Study Sections are composed of peers or colleagues, if you will, of applicants, selected on the basis of their scientific and academic qualifications. The Study Section member of today is the applicant of yesterday or of tomorrow. The criteria for approval or disapproval of applications are really the policies of any university: Is the idea sound and is there evidence that the applicant can pursue it to a logical end-point? Are facilities adequate? Will his interests and those of his institution be well served? And finally, is this a potential contribution to knowledge in a particular field? The Study Sections concern

themselves with the scientific merits of applications. The Councils, composed of scientists and laity, concern themselves largely with policy. Procedures and policies for training grants are exactly comparable with those for research.

There is every evidence that the academic institutions of this country play a major role in determining the manner in which money earmarked for the medical sciences shall be disbursed, and the conditions for such disbursements. Any faults which exist are largely the result of our own limitations as investigators and teachers in evaluating ideas and people.

In the administrative structures of universities there is an alarming trend to exercise unreasonable control over faculty members in seeking and using extramural funds. Policies generated by nonteaching officials in university administration are passed down to the faculty. These begin with restrictions upon which sources of aid may be sought, involve committees and departmental chairmen who pass judgment on the research plans of fellow workers. Resolution of intramural obstacles is needed as the government explores possibilities for further grants to institutions rather than to individuals. As much as teachers and investigators dislike short-term government support given piecemeal, at least in this system we are free agents, in fair competition. Long-term support by block grants to institutions must provide that the investigators who eventually use this support are capable of making important contributions to scientific progress.

Six seminars on various aspects of teaching were held during Saturday morning. Summations of the discussion at each, as prepared by seminar officers, were presented and discussed in the Plenary Session on Saturday afternoon, January 23. Seminar titles, officers, members and summations are presented below.

SEMINARS ON TEACHING OF DIABETES

I. *Integration of Basic Science and Clinical Teaching*

Chairman: Arnold Lazarow, University of Minnesota Medical School. Recorder: Frederick C. Goetz, University of Minnesota Medical School. Members: Paul Beigelman, University of Southern California School of Medicine; Burt Cochran, College of Medical Evangelists; A. Gorman Hills, University of Miami School of Medicine; E. Henry Keutmann, University of Rochester School of Medicine and Dentistry; Robert L. Jackson, University of Missouri School of Medicine; Robert H. Williams, University of Washington School of Medicine.

This was a seminar on desegregation. Fortunately, all members assumed, tacitly and from the outset, that integration of clinical and basic science teaching is desirable, both in diabetes teaching and in general medicine. Four phases of medical teaching were discussed: undergraduate teaching; hospital training (internship and residency); advanced training for research; and postgraduate teaching. Concepts were exchanged concerning present materials available in the schools known to members of the group. Areas in which deficiencies exist were pointed out, along with the best means to reach the desirable goal of integration. Some of these comments will be pertinent to the interests of the seminars on Conferences and on Research Training.

The substrate of the problem is clearly the medical student. Within one school, and between one school and another, there are vast differences in the interests, abilities and eventual careers of students. As time passes, most students seem to pass through a more or less predictable change in emotional and intellectual direction. During the first two years in medical school they have a general, vague desire to learn clinical medicine, but the goal is remote. At this time they are most susceptible to the inherent interest of the basic sciences as disciplines in themselves. At the end of the second year there is usually a transition to clinical studies. From here through the first or second year of residency training students are immersed in the acquisition of clinical knowledge. The majority enter practice and subsequent formal training consists of postgraduate courses and medical meetings. A small number remain close to the medical school for advanced training; some return for formal work in a basic field, in preparation for careers in teaching and research. They combine interests and divide time between basic and clinical fields.

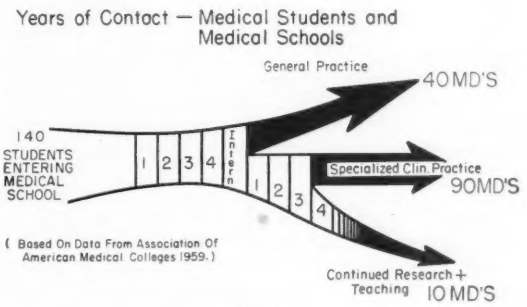

Years of Contact — Medical Students and Medical Schools
General Practice
40 MD'S
140 STUDENTS ENTERING MEDICAL SCHOOL
1 2 3 4 Intern
Specialized Clin. Practice
90 MD'S
1 2 3 4
(Based On Data From Association Of American Medical Colleges 1959.)
Continued Research + Teaching
10 MD'S

FIGURE 1

The medical school represents the medium, the enzyme, and the co-factors in the reaction between the fundamental and applied sciences in teaching. Certain physical and departmental characteristics in the schools bear directly on the problems of integration:

1. Physical locations may interfere with ready communication between departments. The school may be so big that communication even within a given department is difficult.

2. The knotty problems arising when basic scientists work and hold appointment in clinical departments may help or impede integration of teaching, depending upon the relationships of these workers to the basic science departments concerned. There is danger that such persons may gradually recede from the main current of work in their own fields and that their scientific growth may halt. First-rate people given adequate freedom and support will work effectively, however, no matter what the department. There was some fairly sharp disagreement on this point.

3. Intense efforts have been made in a number of schools to break down compartmental thinking in both student and faculty by curriculum revisions which integrate various basic science divisions. Such curricula may offer the best safeguard against narrow-mindedness.

4. While encouraging the principle of integration deans and department heads may not allow sufficient time for the faculty to carry it out. Good correlative conferences and clinics take good planning. A poorly planned conference is worse than none. More important than any of these considerations, however, is the underlying temperament and viewpoint of

the teacher himself. Basic scientists must be interested in (and not afraid of) clinical discussions, and clinicians must acquire a speaking acquaintance with the basic sciences, even if they cannot know them well. Even under the most favorable conditions only a small portion of current teachers can represent both disciplines. Clinical orientation for basic scientists and fundamental training for clinicians must be sought in faculty development. The goal, then, is to provide an environment most likely to produce in the student an open mind. This is a mind that makes its own correlations habitually, breaking down artificial barriers. It should not passively accept what is offered, like a sponge.

What deficiencies must be recognized in entering students? Intellectual independence is not possible for many of them. Most seminar members ruefully accepted the need for guideposts such as mimeographed outlines, didactic lectures, etc., to keep the average student from floundering. The student's limited time requires that material be predigested for him.

What deficiencies exist within present schools, and what measures are most likely to provide integration of teaching for all students, and maximum stimulation for the gifted?

1. It seems likely that one department knows far too little of what is taught by other departments in related fields. Interdepartmental knowledge of the curriculum is highly desirable, both to avoid gross gaps in teaching and to avoid excessive duplication (some planned duplication is desirable). This would seem to be a primary obligation of any faculty which is not assumed in many schools.

2. Current efforts toward curricular integration of teaching probably will produce better integrated teachers and, therefore, better integrated students. Both the curriculum itself and, more important, the interdepartmental discussions required for the adoption of any new plan, break down barriers between departments and individuals. No matter what the immediate outcome, review of curriculum is desirable.

3. In preclinical years, particularly in the "classical" curriculum, there is real virtue in the "correlation clinic," in which biochemical and physiological knowledge is applied directly to clinical problems. Such dramatizations of basic knowledge are generally successful in stimulating the student's interest. In fact, such stimulants are so effective that they may easily be overdone, distracting students too soon from the intrinsic value of the basic field.

4. In clinical years (from the third year of medical school through the first year of residency, at least) a combined clinical-fundamental conference of some sort is a most effective way of integrating teaching. It is highly desirable that members of preclinical departments participate actively in such conferences. Their mere presence, even if they do not talk at all, has a salutary effect in several ways. The clinician must plan the major role, however, in relating clinical and basic concepts. Otherwise many students, even the most gifted, may simply absent themselves physically or mentally with the comment "Don't bother me with this stuff—I'm going to be a physician." Some reservations were expressed about the efficiency of the correlation conference or panel from the point of view of the teacher's time. This conflict appears to be insoluble. *If good teaching takes time, time to teach must be taken.*

5. The clinician who is able to bring up relevant ideas from the basic sciences in small groups at the bedside is as effective there as in formally planned conferences with basic scientists present. Basic scientists are sometimes invited into ward rounds, but this is unlikely to be a frequent practice for practical reasons of time and talent.

6. Student research fellowships are highly effective in promoting decompartmentalization between preclinical and clinical departments.

7. The value of postgraduate teaching for the benefit of the physician in practice is difficult to assess. At its best it reaches only a small number of practicing physicians. At its worst, it may only refresh temporarily without really correcting a deficiency.

Conclusions: Compartmentalization of mind in student and faculty must be combated at all stages in the student's training, although the usual student's lack of graduate school maturity must be recognized. Changes in curriculum may prove eventually to be important in promoting desegregation. More important, however, is a constant awareness by the faculty of the urgent need for good communication between departments and individuals. The clinical conference is one of the most effective methods of integration, but it can be overdone in the first year or two of medical school. In clinical phases of teaching it is most effective if clinicians introduce the basic sciences into discussions. Underlying all this, however, is the need for deans, department heads and other administrators to share enthusiasm for such goals and to provide time enough for faculties to work toward them.

II. *Organization and Conduct of Teaching with Inpatients*

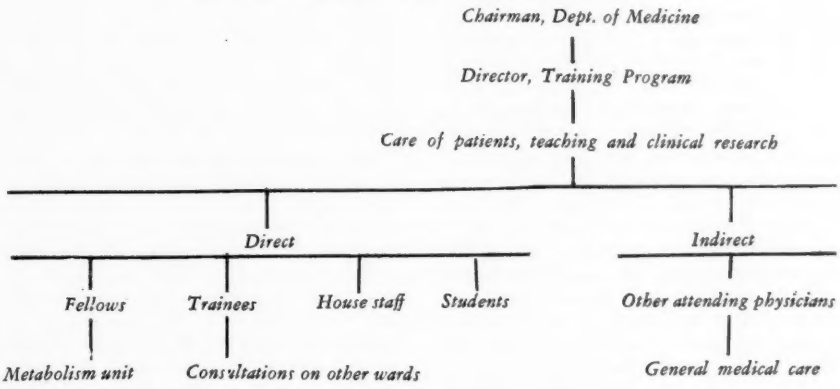
Chairman: George J. Hamwi, Ohio State University College of Medicine. Recorder: Harvey C. Knowles, Jr., University of Cincinnati College of Medicine. Members: Jerome W. Conn, University of Michigan Medical School; Harold Dobson, Baylor University College of Medicine; Lillian Haddock, University of Puerto Rico School of Medicine; Jean M. Hawkes, University of Tennessee College of Medicine; H. B. Mulholland, NIAMD Training Grant Committee; T. E. Prout, Johns Hopkins University School of Medicine; Leon Smelo, Council, American Diabetes Association; H. St. George Tucker, Medical College of Virginia; Kelly M. West, University of Oklahoma School of Medicine; Ernest H. Yount, Bowman Gray School of Medicine of Wake Forest College.

This seminar dealt with the conduct of inpatient teaching of medical students, house staff, trainees, fellows, practicing physicians, and ancillary personnel.

The general standards and quality of diabetes teaching and therapy should be determined by a director of training in metabolism, with assistance if possible. Information should be disseminated throughout the institution to produce as much homogeneity as possible to those to be trained. The chart on page 409 indicates proper organizational channels, with emphasis on therapy for inpatients.

The influence of the teaching unit in the study and management of the patient thus will be felt both directly and indirectly. This scheme will establish a chain of responsibility for patient care from intern to department chairman.

Five to 10 per cent of the patients in a general hospital are diabetic, thus affording adequate diabetic clinical material. The spectrum of pathology found in diabetics is satisfactory except in areas where a limited number of patients are admitted in diabetic acidosis. A major current problem in inpatient



teaching and research is the lack of economic support and absence of physical facilities for intensive study of metabolic patients.

The advantages and disadvantages of geographic concentration of subspecialty beds were discussed. The advantages of a localized service were considered to be efficiency of actual patient care, convenience of teaching, greater concentration of attention of personnel on one disorder, constant accessibility of the faculty members on the service to students and house staff, and easier follow-up care by service physicians. Disadvantages include fragmentation of teaching, preoccupation with the patient's diabetes alone, dilution of diabetic patients in general medical wards, and decreased exposure of the student to other attending physicians. Segregation of beds only for the purpose of intensive investigation was recommended by a vote of eight to four.

Diabetic and other inpatients should be utilized in teaching of *clinical clerks* in the third year primarily to stress the importance of history-taking and physical examination. Diabetes teaching should be incidental at this stage. It should be stressed only after the disciplines of thorough case study have been mastered. Didactic lectures are of limited value, but seminars are of great importance. In many institutions the major teaching of the senior student is done in the outpatient clinics and this phase of education was not discussed in this seminar. Bedside and clinic teaching of diabetes should be the responsibility of the director of diabetes training or his delegate.

The need for enriching the experience of the exceptional or honor student was discussed. An honors program which permits elective time to be spent in the metabolic or some other research unit should be encouraged. It is true, also, that the poor student must be competent before he is allowed to graduate. Such students require special attention of a different kind.

The house staff should be taught on general medical wards, but rotated through metabolic wards and conferences. Their knowledge of diabetes will be enhanced by consultation with members of the diabetes training program and contemporaries.

The first year of a trainee in diabetes should be spent under the close supervision of the director or his assistant. In the second year the trainee can make major contributions to teaching and consultation in diabetes. Research in metabolism should occupy the balance of his time. Ideally, he is a major integrating force in the activities in diabetes in the metabolic section and the general medical wards.

Attending physicians who serve on general medical wards learn indirectly in consultations with members of the metabolic training unit, and by attendance and participation in conferences and rounds. A superior training program enhances their knowledge and capacity, particularly if unrestrained consultation is the rule.

Finally, it was thought desirable that the flexibility of training programs as indicated by recent trends would be safeguarded in the future to permit optimal adaptation of funds to fit local problems.

III. *Use of the Outpatient Clinics*

Chairman: Max Miller, Western Reserve University School of Medicine. Recorder: Robert C. Hardin, State University of Iowa College of Medicine. Members: Denis Abelson, Yale University School of Medicine; John J. Canary, Georgetown University School of Medicine; Norman W. Carter, University of Texas Southwestern Medical School; David M. Hurwitz, Harvard Medical School, Boston City Hospital; Francis D. W. Lukens, Council, American Diabetes Association; Harry McPherson, Duke University School of Medicine; T. B. Schwartz, University of Illinois College of Medicine; Laurentius Underdahl, Council, American Diabetes Association.

The organization of a diabetes outpatient clinic revolves around the Program Director. He should be a staff member with personal interest in the field and his appointment should be on a long-term basis. His is the focal role of providing the continuity so necessary in the management and teaching of chronic disease. His interest and permanence will serve to enhance his effectiveness and the establishment of administrative rapport with the director of the entire outpatient department, the department chairman, and the clinic or hospital administration. Clear definition of policy will result, without rigidity, and the difficulties inherent in formulation of policy by those not intimately concerned with the clinic operation. Such a climate provides improvement in teaching, organization of research and standards of patient care.

The duties, the time assignment, and the number of other members of the clinic staff will be determined by the size and scope of clinic activities. Services of dietitians, nurses, secretaries and social workers are usually necessary. Although the services available to the diabetes clinic vary from one

institution to another, these should be enough to permit coordination of all clinic activities and integration with inpatient services. An excellent example is the dietitian who must teach the patient, help with teaching of students and staff, and provide continuity of the patient's dietary management as he moves from clinic to inpatient status to home. Although an ideal arrangement of rooms and provision for orderly patient flow are difficult to achieve, particularly in older buildings, the geographic arrangement of the clinic should be planned carefully. Goals should be set and plans made when remodeling or new construction is contemplated.

Selection of patients has important implications for teaching and research. It is most often determined by the nature of the community population, as modified by clinic and hospital policies and the economic status of available patients. This selection needs study for it determines in good part the complexion of the clinic population. Plans for management must take into consideration language barriers, racial customs and food habits. These, in turn, affect staff structure and formulation of policy.

Another clinic problem is continuity of care. Research programs in chronic disease demand stability of the patient population, and teaching is improved when patients visit clinics repeatedly. All effective means must be employed to keep patients under observation. In part, stability of staff will provide patients with a sense of continued care. From the standpoint of teaching, continuity is more difficult. House staff and students should be assigned for periods as long as possible, so they may better understand the natural history of diabetes. The outclinic is an excellent place for teaching about chronic disease. Long-term complications become clearer and problems of intercurrent and multiple disease status get appropriate consideration.

Attention should be focused on the objectives of the teaching program. It is not enough to assign patients to a student. His load should be adjusted to permit time for instruction. This means that *there must be teachers who have time to teach.* Such an objective determines admission policies, as well as the size of the professional staff.

The outpatient clinic is an excellent place for patient-oriented conferences. Student and house-staff teaching may be strengthened by formal and semiformal small group sessions. Basic sciences should be integrated with clinical instruction. The inclusion of basic scientists on the clinic staff is an excellent means of providing integrated teaching. They should be assigned to the clinic for a definite period of time, and participate in patient care as well as teaching.

The plan of education for trainees should be fitted to individual needs but should always include clinical experience. Observation of patients should be continued over long periods even though the number of hours each week devoted to this type of activity may be small. It should be continued throughout the entire period of the training.

If exemplary patient care and teaching of students, residents and fellows are to be carried out in an ambulatory clinic it is essential that research concerned with problems of diabetes becomes an integral function. The dramatic improvement in the wards of teaching hospitals when these three activities are combined in a single area makes this clear. A truly scientific discussion of the problems seen in outpatients focuses attention on the major problems of diabetes that cry for solution, stimulates interest in all clinic personnel who take part in the research, provides critical appraisal of the methods currently used in routine practice, and inevitably tends to improve standards in all other areas. Progressive clinical instructors become discontented when patient care and teaching are inferior.

What kind of research in diabetes is appropriate for outclinics? Delineation of the natural history of diabetes, particularly with regard to the onset and progression of degenerative complications, can be a major contribution. Patient care must be of such high caliber that long-term follow-up is facilitated. Standard criteria and uniform collection of data must be incorporated into the procedures. Accuracy and validity of data must be assessed properly if the significance of changes is to be determined. Modern methods of record-keeping and use of the new devices for retrieving and sorting data involving large numbers of variables may become necessary. Research of this sort provides an ideal frame-work for critical evaluation of new methods of therapy. Tabular and graphic representations of data give students, residents and fellows a much more comprehensive picture of diabetes than they see in the hospital.

Conclusions: Training of physicians in diabetes must involve the use of facilities for treating long-term illness. Such facilities should be under the direction of a person with authority and responsibility. They must be primarily concerned with diabetes and should be an integral part of the entire diabetes program in the teaching institution. Immediate and long-range policies must be clearly defined. Adequate numbers of personnel (both medical and ancillary) must be provided, and the patient load must be controlled in order that good care and adequate teaching at all levels can be given. Continuity of training, and healthy physician-patient relations are of vital importance. Objectives in teaching at student, resident and fellowship levels should be defined clearly, because differences in approach are necessary. Research appropriate to horizontal study of long-term illness should be an integral function of every teaching clinic.

IV. *Lectures and Conferences*

Chairman: Ben I. Heller, University of Arkansas School of Medicine. Recorder: William Daughaday, Washington University School of Medicine. Members: Frank N. Allan, American Diabetes Association; Louis K. Alpert, George Washington University School of Medicine; Joseph T. Beardwood, Jr., Council, American Diabetes Association; Arthur R. Colwell, Sr., Northwestern University Medical School; W. D. David, U.S. Public Health Service; Norman Engbring, Marquette University School of Medicine; Howard F. Root, New England Deaconess Hospital; Ethan A. H. Sims, University of Vermont School of Medicine; Albert Weinstein, Vanderbilt University School of Medicine.

The greatest variation in teaching practices is found in the usage of lectures in medical education. Differences in educational philosophy of individual medical schools account for this. At one extreme, lecture material in diabetes and other clinical subjects is confined to the second year, with almost exclusive attention to pathologic physiology and mechanisms of disease. In other schools there is a real effort to provide lectures containing a more comprehensive consideration of the diagnostic and therapeutic aspects of diabetes. One school de-

votes fifteen hours of didactic time in the senior year to such teaching.

The pendulum may have swung too far away from the use of lectures. Some of their advantages are being overlooked, for example, the opportunity for truly effective teachers to present their views to the entire student body; lectures permit condensed presentation of vocabulary, classifications and relationships.

The effectiveness of lectures as a means of clinical teaching appears to decrease as clinical maturity of the student develops. Formal lectures primarily for house staff and fellows have proved to be generally unsatisfactory. Exception to this view was taken by several representatives of institutions not containing undergraduate students, such as postgraduate medical schools and large private clinics. Here, the interest in given subjects may be higher, and other educational activities competing for time considerably less than in clinical clerkships. In such circumstances, organized lecture programs are sometimes very effective. As in other areas, the method of teaching is probably less important than the skill of the teacher.

Departments of medicine in some schools are becoming increasingly responsible for teaching content formerly included in courses of biochemistry and physiology. Tremendous growth in those fields has made the available time inadequate. The interrelation of biochemistry and physiology with clinical material must be dealt with in the clinical curriculum, either by a cooperative teaching effort or by departments of medicine. Diabetes training grants are contributing heavily in this respect by training faculty with both preclinical and clinical insight, so necessary for good correlative teaching.

Few differences among schools exist in the use of conferences, "metabolic" rounds and seminars as educational devices. Such methods are used extensively. Clinical conferences should utilize patients as the focus of attention. They should not be used merely as springboards for more general discussion. Special lectures by guests, clinical science seminars, and other group discussions provide excellent vehicles for teaching of basic science subjects.

Teaching of nutrition and dietetics in diabetes is usually inadequate, both in undergraduate and postgraduate education. When these subjects are taught in basic science years there appears to be very little carry-over to the clinical years. Lectures and conferences on nutrition and dietetics, although desirable in the clinical years, are insufficient by themselves to permit students and the house officers to manage diets with facility. In some institutions there is very little instruction in dietetics. Knowledge gained in lectures and conferences must be translated into practical terms by actually calculating and constructing diabetic diets and instructing patients in their use. The teaching dietitian is an important member of the educational team only when he functions under the supervision of the responsible physician. Obviously when he is not well informed in the use of diets he cannot be responsible. Small group conferences in dietetics and individual student instruction in relation to the needs of specific patients appear to be the most suitable mechanisms for effective teaching.

There was considerable discussion about the evaluation of the graduating medical student, particularly as to the depth and breadth of knowledge in diabetes mellitus and similar metabolic diseases. In one medical school the problem was approached in two ways. First, senior medical students were quizzed about their basic and clinical knowledge of diabetes. The lack of knowledge about subjects to which they had been repeatedly exposed in lecture was appalling. Second, questionnaires were sent to interns six months after graduation. Answers indicated that the majority felt insecure and inadequately prepared in diabetes, other metabolic diseases and nutrition. Accordingly, the curriculum was revised at this institution three years ago. Comprehensive conferences on diabetes became part of the teaching program of the senior year. Teaching began with a review of the fundamentals of biochemistry and pathologic physiology. It was assumed that students knew little about diabetes and metabolic disease. The results of the curriculum revision were rewarding. Oral examination of senior medical students now indicates considerable improvement in knowledge, and questionnaires indicate more suitable preparation in diabetes and other metabolic diseases.

We must be constantly aware of the results of teaching and provide criteria for evaluation of the finished product. Research in teaching is no less desirable than research in any other subject. Two specific suggestions were made for feedback information. (1) National Board examinations provide the means for comparisons between institutions. Results of various teaching methods can be evaluated by any institution against others using the same examination, and proficiency in one subspecialty area can be compared with that in others within the same school. (2) Questionnaires sent out shortly after graduation and again in five years or so can provide some insight locally. Evaluation of individual teaching programs and the results they achieve might be a fertile field for the Professional Education Committee of the American Diabetes Association.

The impact of NIH training and research grant programs on medical education was discussed. These programs have made important and continuing contributions in the following regard: (1) There is now increased emphasis on diabetes and metabolic diseases in the curriculum, which will stimulate research and lead to improvement in management of patients; (2) as more trainees with skills both in clinical and laboratory disciplines become available the number of full-time faculty members to bridge the gap between basic and clinical sciences will increase, even within departments of medicine. This will lead to better education in diabetes and metabolic disease, whether emphasis in teaching is on didactic methods, small or large conferences, or seminars.

V. *Education of Patients*

Chairman: Peter H. Forsham, University of California School of Medicine. Recorder: Josiah Brown, University of California at Los Angeles School of Medicine. Members: T. S. Danowski, University of Pittsburgh School of Medicine; Kare Gundersen, Tufts University, Boston Dispensary; Blair Holcomb, Council, American Diabetes Association; Robert Leach, Wayne State University College of Medicine; Alexander Marble, NIAMD Training Grant Committee; Henry Oppenheimer, St. Louis University School of Medicine; Gerald T. Perkoff, University of Utah School of Medicine; Hugh Wilkerson, U.S. Public Health Service.

Educational Technics: Multiple technics all combine to make up an optimal teaching program.

Group Teaching: This is the most efficient way of teaching diabetics and much of it may be carried out by technical per-

sonnel. It is important, however, that the physician participate. Where there are trainees they should do likewise, since teaching affords excellent training. The role of the physician should be that of reiterating, correlating and enlarging upon the topics covered by the specialized professional personnel such as nurses, dietitians and house officers.

Manuals: The need for a practical small manual is generally accepted. Some centers have written manuals suited to the particular patient population and slanted along the particular ideas of the faculty group. The vast majority of hospitals do not have such manuals, however. It would be most constructive for the ADA to prepare a practical manual for patients in the form of a loose-leaf book. It must be emphasized that whatever the quality of the manual, the physician must go through it with the patient. It is a supplement to, not a substitute for his teaching responsibility. More comprehensive manuals should be provided for patients who are able to absorb the subject matter of simpler versions.

Visual Aids: These are of increasing importance for patient education. A series of simple educational films, designed for patient use and prepared by the ADA in collaboration with NIH, should be considered. Also, one must consider seriously TV programs in the form of video tapes. In Utah such a TV series for physicians is presently being carried out after the close of the regular program at night.

Living-in Units: A fourteen-bed unit has existed at the Good Samaritan Hospital in Portland, Oregon, for the past eighteen years and recently a forty-bed unit has been created at the New England Deaconess Hospital in Boston. These contain minimum-care beds which are cheaper by $3.00 daily than the lowest cost hospital bed in Boston. Patients do everything themselves and are allowed to go outside. If serious illness supervenes they are transferred to the main hospital. They are taught to take their own insulin injections, and at lunch they sit at a "training table" with a physician who has them weigh out foods to learn their weights and food values. Lectures are given twice daily (morning and afternoon) for five days. The morning lectures are given by physicians and those in the afternoon by technical personnel. Within five days patients learn how to live with diabetes under ambulatory conditions. This arrangement is deemed most desirable: It should be developed throughout the country. Such a unit may be used as a minimum-care convalescent ward in a general hospital, in which case only a part of it would be occupied by diabetics. The method obviously is most suitable where a fairly active practice in diabetes exists.

Subject Matter: In teaching diabetic patients simplicity and repetition are of great importance. Other members of the family should be educated to make it easier for the patient and to allow the family to act if the patient becomes disabled.

A survey of the pathophysiology of diabetes should be taken up first in teaching. Understanding of the disease is essential for optimal treatment. Complications should be dealt with frankly and without exaggeration, chiefly to accentuate the need for continuous control. The capacity of the patient, both intellectual and physical, should be the only limit to the content of the material that is taught. The most important aspect of diabetes teaching is continuity. This may be achieved by monthly classes, by monthly bulletins (used by certain groups) and by frequent return visits to the physician. In all methods training in addition to treatment is the goal. A well-trained patient need not lean heavily on the physician.

The use of insulin should be taught to every patient. It is easier for him to accept it if necessary later. In emergencies, the patient who has been trained in its use might administer it to himself. Insulin usage should be taught by specially trained personnel. The insulin syringe should be kept in alcohol and both syringe and container boiled once a week. Portable carriers are very convenient. Every patient should be notified of their existence.

Oral hypoglycemic agents should be described as being capable of controlling hyperglycemia in selected cases. It may be dangerous to try to substitute them for insulin.

Testing of urine should be done on premeal specimens. Patients preferably should void one-half hour before collecting the specimens. This should be done four times a day and every day during the initial period of training. Eventually it may be done only one day weekly. Morning and afternoon specimens may be watched if the patient is well-regulated and/or very busy. Preferred technics are: Benedict's solution (still the most reliable); Clinitest, which is subject to deterioration unless sealed in foil, which makes it expensive; various tapes, which should be used only to demonstrate the presence or absence of urine sugar. Acetone testing by tablet or Ketostix was advocated to assess the seriousness of marked urine sugar excretion.

Diet System: A strict diet on initiation of therapy was approved unanimously. This has permanent educational value. Some physicians feel that weighing food is of the utmost importance initially; others felt that a visual estimate is sufficient. The patient must be taught to know what he is eating and to hold the food intake constant from day to day. Exchange lists are deemed satisfactory, but because of their great simplicity, most physicians no longer bother to determine the exact composition. This has mechanical implications which interfere with the best in teaching.

General Health: Every diabetic should have suitable identification. The ADA and similar identification cards do not serve the purpose when victims of hypoglycemia are picked up by police, since officers are not permitted to open wallets and search without a special warrant. Diabetic patients should carry suitable identification *tags,* bearing minimum information, namely, the existence of diabetes, the approximate insulin dosage and the type of diet.

Foot hygiene was considered most important. Patients, unless they are obese, blind or anesthetic, should be taught how to cut their own toenails. The attendance of a good chiropodist in the clinic is deemed an asset.

In terms of job counseling, certain diabetic patients should avoid hazardous occupations and those involving heavy physical exertion. Ideally, the patient should be part of a small business with a number of co-workers who might deputize for him when required.

Conclusions: The ideal teaching program for diabetics is one which is repetitive and continuous. Regularity in the life of the diabetic patient can be maintained only if he is considered as a true partner of his physician, and if the physician, in turn, is fully aware of his responsibility to train his patients well.

VI. *Research Training*

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Bent Brigham Hospital. Recorder: Richard A. Field, Massachusetts General Hospital. Members: Samuel P. Asper, Jr., NIAMD Training Grant Committee; J. Thomas August, Stanford University School of Medicine; John F. Buse, Medical College of South Carolina; Piero P. Foa, Chicago Medical School; Philip M. Henneman, Seton Hall College of Medicine and Dentistry; S. Richardson Hill, Jr., Medical College of Alabama; Vincent C. Kelley, University of Washington School of Medicine; Laurance W. Kinsell, Council, American Diabetes Association; Julian I. Kitay, University of Virginia School of Medicine.

Definition of Research Training: Research training can be defined as the development of an attitude of curiosity, enrichment of the fund of information, and imparting of technical instruction to a person with latent talent for teaching and research. In diabetes this will enable him to make scientific inquiry in the broad field of intermediary metabolism, possibly to uncover new valid information. It is a process by which a knowledgeable and experienced instructor enters a relationship with a well-motivated student in order to equip him with facts and experience which will bring the student to a level of competence which permits independent productivity. Research training cannot be accomplished by methods of instruction at a distance. Such methods may suffice for static fields of knowledge where original efforts are not necessarily required of the student. Training in a research endeavor, if it is to be successful, must be individualized. It depends heavily on the self-engendered interests of the pupil. It creates a time-consuming and at times difficult responsibility for the mentor.

Desirability of Research Training for Trainees of the Program: Research training should be an integral part of the experience offered trainees in training grant programs. Despite this agreement on principle, it was obvious that no one method or philosophy of research training could be devised which would be applicable to all institutions holding training grants in diabetes currently. No single method can be used as a criterion for the selection of institutions for future programs. There was controversy as to what the desirable goals for research training should be and what proportion of the trainee's time and energy should properly be directed in such a manner. Agreement on these questions was not possible but certain definite ideas were crystallized which seemed inherent in the general NIH training programs.

1. Although there need be no operative distinction between research fellows and trainees, there is an important distinction as to the obligation of the institution toward the trainee. To the trainee, research training need not be the initial step of a lifelong pursuit of investigation, although in some cases it might become such. By virtue of their traditional interests certain institutions might be oriented toward patient care, while others have a large investment in investigation. An essential feature of any program, however, is to include a suitable amount of research training.

2. The trainee should develop his own research problem under skillful guidance. The conditions of his experience and the examples set by permanent members of his group should be such that his interests and appetite can be satisfied in no other way than to try his hand at some investigative problem, whether clinical or fundamental.

Impact of Research Training on Teaching: Research training has certainly made a startling and substantial impact on the over-all teaching, patient care, and interest of paramedical personnel. The investigative role of the trainee has proved effective in his consulting contacts with the house staff, part-time clinicians and attending staff. The shaping of attitudes of those he contacted proved to be as important as his factual information. A large measure of his success in this function could be traced back clearly to the advantages of the research training he himself enjoyed. This improvement has created problems for the Program Director and his senior staff. Chief among these was the provision of adequate time for supervision of the trainees, and for meeting the demands created by awakened interest in fundamental research. Although each institution meets this problem in an individual way, the obligation to teach and share must be recognized. In some cases it may be done by addition of personnel and in others by adjustment of the research programs of preceptors. A proper balance between expansion of teaching due to the training program and curtailment of other important functions to carry it out has not been easy to find. It was agreed that research training increases demands for time, planning, space, and faculty personnel.

Impact of Training Programs on Research Activities: If the educational impact of research is to be meaningful it is essential that the additional responsibilities of the training program should not decrease the quality of, or time available, for research activities by faculty members. In general, present programs do not represent unduly heavy additional burdens, provided additional full-time personnel become available and the ratio of instructors to trainees remains high. Exceptions were noted, and it was agreed that training programs should provide solutions for administrative or financial problems created by increased training needs and altered research activities. Individuals whose special interest in academic medicine is research should remain closely associated with the training programs. The very real danger of diminishing the value of research programs by diluting the research activities of senior staff and research fellows was recognized.

On the other hand, it was agreed that training programs exert a catalytic effect upon research activities in many institutions by facilitating and broadening contact with clinical medicine. Individuals representing both research and the clinical interests encourage critical attitudes by free communication with each other.

Recommendations: The following recommendations seemed of special importance:

1. The most desirable candidates at any level in training programs are those who seriously contemplate full-time (or at least part-time) research and teaching in their careers. With individuals who contemplate full-time practice careful consideration should be given in each instance to the possibility that exposure to research and teaching might modify those plans. If not, the experience will result in a more critical and fundamental attitude in practice. Such trainees can serve a teaching function in their communities and among practicing colleagues. Further, they become better diagnosticians, because there is no sharp line between clinical investigation and expert diagnostic study. Trainees who are integrated into training programs containing individuals with different backgrounds can make important teaching and research contributions. Special benefit has often come from inclusion of stimulating individu-

als from foreign countries. In such instances unusually well qualified individuals should be selected, preferably with substantial achievements already to their credit.

2. The most desirable institutions for extension of the training grants program would seem to be those which provide active research in carbohydrate and intermediary metabolism. If this is not present, training programs granted to such institutions must provide for launching of such research activities.

3. A training program carries responsibility not only for research training but also for support of the added research undertaken by trainees. This responsibility extends to research activities in the laboratory as well as to those conducted at the bedside. Since quantitative observations on patients provide excellent training in clinical research and metabolism, metabolic ward facilities are of primary importance. Support of an appropriate part of such facilities, especially funds for research beds, should fall within the scope of training programs.

4. Undergraduate students serving full-time research fellowships during free quarters make highly desirable additions to training programs. As in the case of graduate trainees, an exposure to research may "take." If not, better capacity to obtain and interpret facts cannot help but be a consequence.

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Dietary Fat and Hepatic Lipogenesis

R. Hill, J. M. Linazasoro, F. Chevallier and I. L. Chaikoff (*J. Biol. Chem.* 233:305, 1958) have demonstrated an influence of the amount of fat ingested by the rat on hepatic lipogenesis.

The effects of high levels of fat in the diet on the lipogenic capacity of the liver were studied in experiments with intact rats. The animals were fed isocaloric diets containing 0, 5, 10 or 15 per cent of corn oil, for three days. They were then injected with acetate-1-C^{14} and killed one hour later. The livers were removed and analyzed for C^{14}-fatty acids. Again the percentage of C^{14}-fatty acids recovered from the liver decreased as the amount of fat in the diet increased.

These effects of ingested fat upon hepatic lipogenesis occurred without changes in the glycogen and fat content of the liver or in the glucose and lipid content of plasma. Also, in no case was there a decrease in the glycogen content of the liver of rats fed the high fat diets for three days. "Thus, the depressing effect of dietary fat upon hepatic lipogenesis was observed under conditions that allowed for priming of hepatic lipogenesis by carbohydrate."

In view of the influence of insulin on hepatic lipogenesis, the possibility that the depression in lipogenesis produced by a high fat diet might be a result of a relative decrease in available hormone was examined. In normal rats fed on diets containing 50 per cent of glucose, with or without added fat, the administration of two units of insulin twice daily for three days failed to prevent the depression in hepatic lipogenesis induced by a high fat intake.

The results of these experiments indicate that the lipogenic activity of the liver is controlled in some way by the amount of fat ingested and that hepatic lipogenesis is depressed by a high fat intake, even when the diet contains a high percentage of carbohydrate. The mechanism of this adaptive response remains to be explained, but it does not appear to be mediated by the depressing effect of a high-fat intake on insulin production.

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EDITORIAL

SALICYLATES AND CARBOHYDRATE METABOLISM

More than twenty billion aspirin tablets are prescribed and self-prescribed in the United States each year for their analgesic, anti-inflammatory and antipyretic effects. In addition to the common uses and effects of this medicine, the physician interested in diabetes should be familiar with two phenomena produced by large doses of salicylates in humans, (a) the similarity of the toxic syndrome (salicylism) to diabetic keto-acidosis and (b) the hypoglycemic effect of large, sustained doses with its investigational and possibly therapeutic implications.

In a report of a case of salicylism in a five-year-old boy with a presenting picture resembling diabetic keto-acidosis, Cohen[1] discussed the differential diagnosis between the two conditions and reviewed the pertinent literature. Bowen and his associates[2] recommended that salicylate poisoning be considered when one is diagnosing coma, particularly when hyperpnea is a prominent feature. The importance of this consideration is underscored by Glicklich's[3] estimate that 30 per cent of the accidental poisonings treated at the Children's Medical Center in Boston in 1956-57 were due to salicylates. Segar and Holliday[4] have presented an excellent discussion of the clinical and biochemical abnormalities in salicylate intoxication.

Physicians familiar with the variants of diabetic acidosis will not be surprised at the ease with which the diagnosis may be confused. Polydipsia, polyuria, hyperpnea, nausea and vomiting have understandably been regarded as manifestations of diabetic acidosis. To confuse the casual observer still further, Benedict's qualitative sugar reagent is reduced by the degradation products of salicylate,[5] and true hyperglycemia and glycosuria may follow the ingestion of salicylates.[6] Moreover, the ferric chloride diacetic acid test is positive for both diacetic acid and salicylate, the urine showing a deep violet color when the reagent is added. Simply boiling the urine differentiates them in this case, however, since the volatile ketone bodies will disappear whereas the nonvolatile salicylates will continue to give a positive test after boiling. In addition, the presence of tinnitus, muscular irritability, and petechiae (due to hypoprothrombinemia) combined with the absence of extreme dehydration and hepatomegaly may point to a diagnosis of salicylate poisoning which can ultimately be confirmed by the determination of serum salicylate levels.

Gross and Greenberg noted that large doses of salicylates (10 to 12 gm.) were used to lower the blood sugar of diabetic subjects in the late nineteenth century.[7] This treatment was largely abandoned, however, even before the advent of insulin, probably because of the frequent occurrence of vomiting with worsening of the ketosis after such large doses. More recently, Reid, MacDougall, and Andrews[8] have demonstrated a lowering of the fasting blood sugar and disappearance of glycosuria and ketonuria following a short, intensive course of aspirin in mild to moderately "severe" diabetics. These authors also note that the disagreeable symptoms of salicylism make the method of treatment impracticable. Reid and Lightbody,[9] however, in a later publication note that the oral dose required to achieve an effective serum salicylate level varies widely from person to person and that the toxic symptoms can be avoided by reference to serum salicylate levels determined during the first few days of treatment. Hecht and Goldner[10] have extended these recent observations on the hypoglycemic effect of salicylates to normal as well as diabetic subjects.

Although it does not seem likely that aspirin is needed to replace current modes of therapy in diabetes, the authors of these series mention that this medication does have the advantage of being free from the threat of agranulocytosis even when used over long periods. Moreover, Beaser[11] has demonstrated not only an additive, but seemingly a synergistic effect of oral, hypoglycemic agents with different modes of action so that salicylates might have a place as an adjuvant in therapy, as suggested by Stowers.[12] Even if judgment is reserved concerning the ultimate place of aspirin in the therapy of diabetes mellitus, further investigation of their mode of action may serve to illuminate the action of other orally effective agents and, possibly, some of the basic disorders in diabetic metabolism.

Salicylates have been reported to deplete adrenocortical ascorbic acid in the intact[13] but not the hypophysectomized[14] rat. An instance of a "mild Cushing type syndrome" in a child given large doses of salicylate is reported.[15] The concept that salicylates act in some way

to stimulate the adrenal cortex must be critically examined in the light of the results of Peterson, Black, and Bunim[16] who failed to show any increase in the plasma concentration or rate of metabolism of hydrocortisone or corticosterone, or in the urinary excretion of corticosteroids or 17-ketosteroids after salicylate administration. The elevation of 17-hydroxy-corticosteroid in the plasma of patients with salicylate intoxication and in guinea pigs given large doses of salicylate[17] may be a nonspecific stress response or a response seen only after very large doses. No consistent changes were found in the plasma level of 17-hydroxy-corticosteroids in humans given therapeutic doses of aspirin.[18] Smith[19] has further pointed out that the ascorbic acid depletion of the rat adrenal also follows the administration of both meta- and para-hydroxybenzoic acid, neither of which mimics salicylate therapeutically.

Another line of investigation is suggested by the observations that sodium salicylate stimulates the oxygen uptake of several tissues[20] and acts as a peripheral-acting metabolic stimulant.[21] Wolff and his associates[22] present detailed data to demonstrate an "extrathyroidal hypermetabolic" effect of sodium salicylate. That the hypoglycemia following salicylate administration is not solely a result of increased utilization by an induced hypermetabolic state is suggested by the work of Reid.[23] He has demonstrated that dinitrophenol, which shares with salicylate the ability to elevate the metabolic rate and inhibit oxidative phosphorylation, is appreciably less effective as a hypoglycemic agent. Moreover, Stowers[12] has shown that the hypoglycemic effect of calcium salicylate persists after the BMR has returned to normal.

It has been suggested that salicylates produce amelioration of the diabetic state by depleting the glycogen reserves of the liver. There is some modifying evidence of this view in that the reduction of glycosuria in the alloxan-diabetic rat is achieved without reducing the hepatic glycogen, while the hepatic glycogen declines without a change in blood sugar levels after salicylates in the normal rat.[24-26] Hecht and Goldner[10] were able to demonstrate normal glucagon tolerance responses in their human subjects after prolonged and effective treatment with salicylates. There is probably not a simple antagonism with the adrenocortical hormones in respect to glycogenesis since salicylate achieves its effect without affecting the negative nitrogen balance of excessive steroid administration.[27]

Perhaps Stowers' observation[12] that salicylate hypoglycemia is more marked in the fasting than the post-absorptive state can be reconciled without invoking a primary inhibition of hepatic glucose output. Manchester, Randle, and Smith[28] demonstrated that salicylate, like insulin, increases the rate of uptake of glucose by the isolated rat diaphragm. These authors suggest that the mechanism may be the inhibition of the oxidative production of energy-rich phosphate bonds. An increase in muscle utilization of glucose by salicylate is further supported by the demonstration of a rise in the circulating levels of lactate and pyruvate.[29]

Finally, the role of the amount of food ingested on such large doses of salicylate must be evaluated by very careful, perhaps metabolic balance, technics, since it would seem likely that there is a rather profound anorexia in these subjects and all of the authors cited point out that there is a diet of constant composition but it is not clear whether this is proffered or ingested food. The observation of a fairly constant weight over the period of salicylate administration does not eliminate decreased caloric intake as a contributing factor since Lukens and Dohan[30] have observed amelioration of the diabetic state on caloric restriction without weight loss. There was, moreover, a definite weight loss in all the patients who were followed after stopping salicylates so that their constant body weight during the period of the drugs may have been due to expansion of the extracellular fluid, a phenomenon confirmed by Stowers.[12]

The very wide use of salicylates, with and without medical supervision, warrants a wider appreciation of the problem of differential diagnosis from diabetic ketoacidosis. In addition, careful investigation of the endocrine mediation of the effect of salicylates and other orally effective hypoglycemic agents on total metabolism as well as specifically on carbohydrate metabolism would provide useful clues to the mechanism of their action. Finally, as suggested by several authors, the optimal management of the diabetic patient may be achieved by combinations of various hypoglycemic agents if dietary control, weight reduction (when indicated) and muscular work are insufficient to maintain normoglycemia.

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BOOK REVIEWS

REVERSIBLE RENAL INSUFFICIENCY: DIAGNOSIS AND TREATMENT. *By Donald H. Atlas and Peter Gaberman. $7.00, pp. 233, The Williams & Wilkins Company, Baltimore, Maryland, 1958.*

This small volume provides an easy review of much of the available information and current thinking on the subject of renal insufficiency of various origins, chiefly acute tubular necrosis. Examples of renal failure attributed to mercurous chloride, carbon tetrachloride, body fluid depletion, diabetic coma, alkalosis, acidosis, hyperparathyroidism and lupus are described from the authors' experience. Toxemia, cortical necrosis, urinary infection, cerebral salt wastage, epidemic hemorrhagic fever, renal calcification, renal tubular disease, gout, and a host of other precursors of renal failure are also discussed or listed.

Details of biochemical aspects are generally lacking in keeping with the attempt to present the subject in a discursive manner. However, since their own observations on particular entities are generally not given, the development and flow of concepts and information are intermittently halted by the necessity to cite in detail the work of others. Nonetheless the end product is a useful presentation of the problem and the bibliography is adequate for further study. The eight cases of hypercalcemia and sarcoidosis reported by Sholz and Keating are erroneously listed in table 4 as examples of Burnett's syndrome.

PERIPHERAL VASCULAR DISEASES. *By Travis Winsor, M.D., F.A.C.P. $16.50, pp. 845, 435 illustrations, Charles C Thomas, Springfield, Illinois, 1959.*

This is an encyclopedic text presenting a fascinating array of diverse information. As can be expected by those familiar with the author's interests, more than 100 pages are devoted to the governing laws, mechanical construction and operation of medical gadgetry. This is highly recommended reading to all frustrated engineers. Unfortunately the author's dependence on the plethysmogram has so colored the clinical section of the book that it is not too useful to those of us who in the past and in the future will continue to use successfully only our eyes, ears and fingers in examining the patient.

The lavish use of excellent diagrammatic illustrations will help the student to understand the anatomy and physiology of the vascular structures and their diseases.

The author has included almost all theories of causation and modalities for therapy without critically selecting and presenting the very few which have proved useful.

This reviewer believes that hemoptysis should be mentioned as a symptom of pulmonary infarction, that enzymatic debridement of ischemic ulcers is positively harmful, and that four inches elevation of the feet in treating thrombophlebitis is sending a small boy to do a man's work.

In summary: The first half of the text is excellent and rewarding reading. The second or clinical half should be absorbed through a critical filter.

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1885-1959

Randall G. Sprague, M.D., Rochester, Minnesota

Dr. Russell Morse Wilder, Sr., died in Rochester, Minnesota, on Dec. 16, 1959, at the age of seventy-four years. He played an important role in the development of the American Diabetes Association and served as its president in 1947. During his professional career he became a figure of international distinction in the field of diabetes, and was widely known for his contributions to nutrition and metabolism. At the time of his death he was an emeritus member of the medical staff of the Mayo Clinic and emeritus Professor of Medicine in the Mayo Foundation, Graduate School, University of Minnesota.

Dr. Wilder was born on Nov. 24, 1885, in Cincinnati, Ohio. In his family were several distinguished physicians and authors, and his two sons who survive him are physicians. In 1907 he was graduated with the degree of Bachelor of Science from the University of Chicago, where the scholarly attributes which were conspicuous in his later professional life were fostered. His college work included a year of study in Heidelberg, Germany. In 1910, while he was a medical student at the University of Chicago, he went to Mexico with Dr. Howard Taylor Ricketts to study typhus fever. Ricketts died of this disease in that year, but Dr. Wilder, with characteristic energy and curiosity, returned to Mexico to carry on the studies Ricketts had initiated. He received the degrees of Doctor of Medicine and Doctor of Philosophy magna cum laude from the University of Chicago in 1912. For standing first in his class he was awarded the Benjamin Rush Gold Medal. In 1914 he studied in Vienna for eight months, principally at the First Medical Clinic under Müller-Deham, who had been one of von Noorden's assistants. There a beginning interest in diabetes grew and found active expression. Upon his return from Vienna he became resident physician in the Presbyterian Hospital of Chicago. This was the first residency to be created in a hospital west of the eastern seaboard. One of the things which attracted Dr. Wilder to the post was the availability of research facilities at the Otho S. A. Sprague Memorial Institute of Rush Medical College of the University of Chicago. With Dr. Rollin T. Woodyatt he investigated the rate of utilization of glucose and ketone acids in dogs, and developed further his interest in clinical and experimental diabetes. These studies were interrupted by service in the Medical Corps of the Army in the First World War. He left the army in 1919 with the grade of captain and with a citation by the commander-in-chief of the American Expeditionary Forces for "exceptionally meritorious and conspicuous service."

In 1919 he became a member of the staff of the Division of Medicine of the Mayo Clinic and Assistant Professor of Medicine in the Mayo Foundation. By then his interest in diabetes was well established and he was placed in charge of all diabetic patients, who, at the time, numbered about 100 a year. In later years the annual number exceeded 2,500. He was promoted to the rank of Associate Professor of Medicine in the Mayo Foundation in 1922.

At the Mayo Clinic he investigated various clinical problems in the field of metabolism and nutrition. He long will be remembered as one of the pioneers in the clinical use of insulin after its discovery by Banting

and Best in 1921. Among his other early contributions was a demonstration of the effectiveness of a ketogenic diet in the treatment of epilepsy. In 1927, with Allan, Power and Robertson, he described the first recorded case in which organic hyperinsulinism was caused by a carcinoma of pancreatic islet tissue with spontaneous production of excessive amounts of insulin.

A considerable number of physicians can trace their interest in diabetes to the inspiration of Dr. Wilder. Over the years he suggested many research problems in the field of metabolism, particularly diabetes, to his graduate students, and he became known for his generosity in giving credit to them and to other collaborators in clinical and laboratory investigation.

In 1929 Dr. Wilder became Professor of Medicine and chairman of the Department of Medicine at the University of Chicago. In addition to clinical practice and teaching he worked there on osteitis fibrosa cystica, obesity, Addison's disease and epilepsy. In 1931 he returned to the Mayo Clinic and became Professor of Medicine in the Mayo Foundation and head of the Department of Medicine of the Mayo Foundation. In the years to follow, with his colleagues and students, he pursued a variety of studies related to diabetes, nutrition and endocrine and metabolic diseases. Among his contributions were studies of the action and clinical use of protamine insulin, introduced in 1936 by Hagedorn, and the demonstration that the course of Addison's disease could be favorably influenced by restriction of the intake of potassium.

He retired from the Mayo Clinic and Mayo Foundation in 1950, and then became the first director of the new National Institute of Arthritis and Metabolic Diseases, where he played a leading role in the development of its resources and activities in the fields of research, support of research and training of specialists in rheumatic and metabolic diseases. The current interest of the Institute in diabetes can be traced in part to his influence. He was a leader in the formulation of the policies and program of the new Clinical Center of the National Institutes of Health at Bethesda, Maryland. Because of ill health he retired as director of the Institute in 1953, and returned to Rochester, Minnesota.

Other activities with the Federal government, particularly during and after the Second World War, added further luster to a career that was already distinguished. He was a member of the Committee on Medicine of the National Research Council from 1940 to 1946, and chairman of that committee in 1940. In 1941 he organized and became chairman of the Food and Nutrition Board on which he served until 1947. In 1943 he was chief of the Civilian Food Requirements Branch of the War Food Administration.

Dr. Wilder occupied many other positions of honor and high responsibility. In 1931 he was appointed a member of the Council on Foods and Nutrition of the American Medical Association, and he served on the council for many years. He was president of the National Vitamin Foundation in 1956. The American Diabetes Association conferred the Banting Medal upon him in 1947, when he was president of the Association. The University of Chicago honored him with the Distinguished Service Medal in 1941 and the Howard Taylor Ricketts Award in 1949. The Medical Alumni Association of the University of Chicago presented him with the honorary gold key in 1955. The American Medical Association gave him the Joseph Goldberger Award in 1954 for his contributions to the field of nutrition, and in 1956 the American Bakers' Association gave him an award in recognition of his leadership in promoting enrichment of white flour and bread with vitamins. He was made a master of the American College of Physicians in 1957 and an honorary member of the American Dietetic Association in 1959.

As a by-product of his many activities in clinical and research medicine he became a notable figure in the field of medical writing, serving at various times on the editorial board of the *Journal of Nutrition* and the *Archives of Internal Medicine,* the editorial committee of *Nutrition Reviews* and as an associate editor of *Public Health Reports.* He contributed more than 250 papers to medical and scientific journals, and was a contributor to several textbooks of medicine and to the *Encyclopaedia Britannica.* He was the author of *A Primer for Diabetic Patients,* published in 1921, with eight subsequent editions; and *Clinical Diabetes Mellitus and Hyperinsulinism,* published in 1940.

Dr. Wilder was loved as a man by those who had the privilege of contact with him. He occupied a position of eminence and respect as physician and investigator. During his career he cared for thousands of diabetic patients, combining devotion, scientific knowledge and warm compassion with firm guidance and sound teaching. He was a kindly gentleman of dignity and personal charm who enriched the lives of his friends, patients and professional associates and the large area of medical science which his career embraced. He is survived by his wife, Lucy Beeler Wilder, and two sons, Dr. Russell Morse Wilder, Jr., and Dr. Thomas Carroll Wilder.

ABSTRACTS

Arduino, Francisco, and Da Cruz Ferreira, Francisco (Moncorvo Filho Hosp., Nat. Faculty of Med., Rio de Janiero, D.F.): CATAMENIA AND MENOPAUSE IN THE DIABETIC AND PREDIABETIC WOMAN. Arq. brasil. Endocrinol. Metab. 7:77-85, April 1958.

A group of 455 diabetic and prediabetic women selected at random were studied with reference to the onset of menarche and menopause and compared with a similar number of controls. In prediabetic and diabetic women menarche occurred earlier and menopause later than in normals. Anticipation of menarche was sharp in the group of prediabetics whose disease appeared early in life. In women who developed diabetes before or after menopause, the latter occurred later than in the average age for the controls. C.A.V.

Arieff, Alex J.; Crawford, James; Adams, J.; and Smith, Dorothy (Northwestern Univ. Med. Sch., Evanston, Ill.): GLUCAGON IN INSULIN COMA THERAPY: ITS USE IN A SMALL PSYCHIATRIC UNIT OF A GENERAL HOSPITAL. Quart. Bull. Northwestern Univ. M. School 34:7-10, Spring 1960.

Glucagon in doses of 2-5 mg. intramuscularly was administered to terminate insulin-induced coma in twenty selected psychiatric patients. A total of 315 episodes of hypoglycemia were treated. Ten to twenty-five minutes were required for consciousness to return after injection of glucagon. Blood glucose rose from a mean of 15 mg. per 100 ml. before glucagon to 44 mg. per 100 ml. afterward. There were no cases of protracted coma after treatment and the necessity for intravenous glucose arose in only one patient. H.L.W.

Ball, Eric G.; and Cooper, Octavia (Dept. of Biological Chemistry, Harvard Medical School, Boston, Mass.): STUDIES ON THE METABOLISM OF ADIPOSE TISSUE. III. THE RESPONSE TO INSULIN BY DIFFERENT TYPES OF ADIPOSE TISSUE AND IN THE PRESENCE OF VARIOUS METABOLITES. J. Biol. Chem. 235:584-88, March 1960.

Addition of insulin to white adipose tissue in the Warburg apparatus produced a conversion of glucose to fatty acid, as well as a marked alteration in the total gas exchange. Addition of insulin to the rat epididymal fat pad produced an increased utilization of glucose, mannose and fructose. There was no consistent response of brown adipose tissue to insulin.

A.R.C., JR.

Balodimos, Marios C.; and Root, Howard F. (Joslin Clinic and New England Deaconess Hosp., Boston): HYPOGLYCEMIC INSULIN REACTIONS WITHOUT WARNING SYMPTOMS. J.A.M.A. 171:261-66, Sept. 19, 1959.

Sudden unconsciousness or grave mental confusion occurred in 116 diabetic patients as a result of hypoglycemic insulin reactions without the usual warning symptoms. The patients had taken insulin for many years and had learned to rely on the specific symptoms and to take carbohydrate to prevent insulin shock. The average duration of the illness in this group was ten years, and sixty-four patients were ten pounds or more underweight, but as individuals the patients were no different from the usual diabetics, and the reason for the absence of premonitory symptoms was not discovered. Possible explanations include cerebral vascular or metabolic changes, diabetic neuropathy involving the autonomic nervous system, a metabolic abnormality in the availability or release of glucose, or epileptic equivalents.

The treatment of the diabetics for the prevention of such reactions must include adjustment of insulin dosage, long-acting insulin in the early part of the day and, usually, short-acting insulin for the later dose, and careful dietary management with frequent between-meal snacks. Diabetic identification cards should be carried in the purse or wallet. B.F.K.

Beckett, A. Gordon; and Lewis, J. G. (Diabetic Res. Dept., Royal Free Hosp., London, England): SERUM MAGNESIUM IN DIABETES MELLITUS. Clin. Sci. 18:597-604, November 1959.

The mean serum magnesium of 100 diabetics was higher than that of thirty-five nondiabetic controls; the magnesium of older diabetics was higher than that of the younger ones. Overweight diabetics had higher serum magnesium levels but this could be explained by the effect of age. The serum magnesium of the young severe diabetic was lower than in nondiabetics and increased with duration of disease. No increase with duration was observed in the older diabetics. The serum magnesium was not related with the presence of vascular disease, its severity, or with the serum cholesterol level. J.A.

Bell, E. T. (Dept. of Path., Univ. of Minnesota, Minneapolis, Minn.): HYALINIZATION OF THE ISLETS OF LANGERHANS IN NONDIABETIC INDIVIDUALS. Am. J. Path. 35:801-05, July-August 1959.

The incidence of hyalinization of islets was studied in 1,661 diabetic patients and in 3,959 nondiabetic individuals. Hyaline islets were not found in either group under the age of twenty years. With increasing age there were more hyaline islets in both groups. Diabetic patients showed a higher percentage of such islets than nondiabetics in all age groups.

Hyaline islets appear to be related to diabetes but cannot be the cause since they were absent in young diabetic patients. Hyaline islets may represent a wear and tear phenomenon increasing with age and accentuated by diabetes. On the other hand, they may be a manifestation of potential diabetes which is not yet clinically evident. H.L.W.

Benjamin, Fred (Dept. Obstetrics and Gynaecology, University of Capetown, Union of South Africa): GLUCOSE TOLERANCE IN DYSFUNCTIONAL UTERINE BLEEDING AND IN CARCINOMA OF ENDOMETRIUM: A PRELIMINARY REPORT. Brit. M. J. 1: 1243-46.

Studies in glucose tolerance have been extended to embrace all cases with abnormal uterine bleeding at the time of the climacteric, both benign and malignant.

Such cases were therefore investigated by glucose tolerance tests and compared with control subjects of the same age group (it is known that age has an important bearing on glucose tolerance). Fifty-two per cent of patients with cancer of the endometrium showed impaired glucose tolerance, compared with

22 per cent in the control group. These figures, on analysis, are significant statistically.

Patients with proved benign glandular hyperplasia were similarly investigated and compared with controls (both normal subjects and patients with uterine bleeding due to other causes). The incidence of abnormal glucose tolerance (84 per cent) in cases of benign glandular hyperplasia was found to be striking and much higher than in the two control groups and higher than in cases of cancer of the endometrium. These figures are very significant statistically. J.A.

Bernstein, Donald E. (Metabolic Research, Mount Zion Hosp., San Francisco, Calif.): VASCULAR EXCLUSION OF THE LIVER: ITS INFLUENCE ON GLUCOSE METABOLISM. Endocrinology 66:783-85, May 1960.

Vascular by-pass of the liver in the rat prevents the hyperglycemic effect of epinephrine and the late return toward preinjection levels of blood sugar following administration of insulin. In fact, half of the animals with hepatic by-pass died in hypoglycemia whereas no control animals succumbed after insulin. The production of bile and the clearance of bromsulphalein are also interfered with by vascular hepatic by-pass. In view of these findings it is suggested that the hepatic vascular by-pass might be substituted for the more traumatic hepatectomy in studying the function of the liver in the experimental animal. H.L.W.

Berson, Solomon A.; and Yalow, Rosalyn S. (Radioisotope Service, Veterans Administration Hosp., Bronx, New York): QUANTITATIVE ASPECTS OF THE REACTION BETWEEN INSULIN-BINDING ANTIBODY. J. Clin. Invest. 38:1996-2016, November 1959.

The author analyzed the kinetics of antibody-antigen binding and dissociation in systems involving crystalline beef insulin-I^{131} and antibodies from antisera from insulin resistant and nonresistant human diabetics. The experiments were conducted over a wide range of concentrations of antibody and antigen.

The results in terms of equilibrium constants indicated that insulin was univalent in its reaction with antibody and that antibody had at at least two possible combining sites with different binding capacities for insulin.

The authors discussed the clinical implications, including the possibility that the insulin binding phenomenon could be responsible for the increased insulin requirements in patients with insulin resistance. S.B.B.

Berson, Solomon A.; and Yalow, Rosalyn S. (Radioisotope Service, Veterans Administration Hosp., Bronx, New York): SPECIES-SPECIFICITY OF HUMAN ANTI-BEEF, PORK INSULIN SERUM. J. Clin. Invest. 38:2017-25, November 1959.

The binding qualities as well as cross reactions in antibody relationships were studied with a variety of I^{131}-labeled insulins: pork, sheep, beef and beef desamido insulins. Beef and sheep insulins were bound more closely than pork or horse insulins.

The results were analyzed and the area of differences in amino acid sequence in the A chain of the insulin molecule is indicated as the site of antigen-antibody activity. However, further work is necessary to settle the matter definitely. S.B.B.

Best, Charles H. (The Dept. of Physiol. and the Banting and Best Dept. of Med. Research, University of Toronto, Toronto, Canada): DIABETES SINCE NINETEEN HUNDRED AND TWENTY. Canad. M. A. J. 82:1061-66, May 21, 1960.

Dr. Best gives a short personal account of his discovery of insulin with Dr. Banting, and a general review of the field of diabetes and carbohydrate metabolism in the intervening years. S.B.B.

Bousvaros, G. A. (Dept. Clinical Therapeutics, University of Athens Med. School, Athens, Greece): HYPOGLYCAEMIA IN METASTATIC FIBROSARCOMA OF THE LIVER. Brit. M. J. 1: 836-38, March 19, 1960.

A case of hypoglycemia associated with metastatic fibrosarcoma of the liver is presented. The subject was a known diabetic and had been treated with daily insulin for six years. For four months previous to admission to the hospital his insulin requirements had been decreasing and at this time he was on 20 units of protamine insulin on alternate days. J.A.

Brown, George; Zoidis, John; and Spring, Maxwell (Diabetes Clin. and Dept. of Medicine, Bronx Hosp., New York): HEPATIC DAMAGE DURING CHLORPROPAMIDE THERAPY. J.A.M.A. 170:2085-88, Aug. 22, 1959.

Hepatic damage occurred in three out of forty-nine patients employed in a clinical trial of chlorpropamide (Diabinese) therapy. The jaundice which occurred in two of the three cases was demonstrated to be due to intracanalicular bile stasis. This could not be shown in the third case, where a sharp rise in the alkaline phosphatase level occurred without jaundice; but the elevation in the alkaline phosphatase level and the abnormal retention of sulfobromophthalein suggest that the same mechanism was operative. The pathology revealed by biopsy was minimal in all three cases and not as severe as the liver function abnormalities would have indicated. Complete recovery occurred in all. It is suggested that reaction may occur more frequently when the dosage of chlorpropamide exceeds 0.5 gm. daily. Its use should be monitored by periodic determinations of the alkaline phosphatase level for the first six weeks. B.F.K.

Cahill, George F., Jr.; Leboeuf, Bernard; and Flinn, Robert B. (Dept. of Medicine, Harvard Medical School; Peter Bent Brigham Hosp.; Baker Clinic Res. Lab., New England Deaconess Hosp., Boston): STUDIES ON RAT ADIPOSE TISSUE IN VITRO. VI. EFFECT OF EPINEPHRINE ON GLUCOSE METABOLISM. J. Biol. Chem. 235:1246-50, May 1960.

Epinephrine produced an increased incorporation of glucose C^{14}-labeled carbon into glyceride-glycerol in the rat epididymal fat pad. Both glucose uptake and CO_2 formation from glucose carbon were increased. The fatty acid synthesis stimulated by insulin was reduced by epinephrine. Epinephrine mobilizes fatty acid from adipose tissue primarily by accelerating triglyceride lipolysis, and it is possible that the increase in free fatty acids resulting from lipolysis after epinephrine administration is the cause of the accompanying changes in glucose metabolism. A.R.C., JR.

Claye, Andrew M.; and Craig, W. S. (Dept. of Obstetrics and Gynaecology and the Dept. of Paediatrics and Child Health, University of Leeds, England): PREGNANCY COMPLICATED BY DIABETES MELLITUS: A STUDY IN COMBINED OBSTETRIC AND PAEDIATRIC MANAGEMENT. Arch. Dis. Childhood 34:312-17, August 1959.

The authors present a study of ninety-four pregnancies in diabetic mothers during a period of eleven years. The infant and maternal morbidity and mortality are analyzed and compared to the pregnancies in nondiabetic mothers during the same period. The obstetric and pediatric care were considered to be optimal but it was found that it was not possible to

reduce perinatal mortality to a level comparable to the nondiabetic population. The neonatal mortality was substantially higher in spontaneous deliveries as compared to those in which pregnancy was terminated either by induction or by cesarean section. No difference in mortality was observed between the induction group and the section group; however, these groups are not comparable, as the indication for the two types of treatment were different. The incidence of congenital anomalies was 13 per cent in the live births of diabetic mothers as compared to 3 per cent in the nondiabetic group, cardiovascular anomalies accounting for half of the total, and also accounting for two of the neonatal deaths.

It could not be shown that the risk of prematurity was greater in the diabetic group than in nondiabetics, a finding which is thought to support the views of those who recommend early intervention in pregnancies of diabetic mothers. The authors feel that had all pregnancies been terminated at thirty-five weeks more babies might have been born alive. All the neonatal deaths were accounted for by cardiac anomalies, vascular crises, and hyaline membrane disease. There were thirty-one cases of superficial skin infection in the seventy-five liveborn babies in the series and forty-eight of the group were found to have enlarged livers. Abnormal weight loss in the newborn period was not frequently encountered in this series. The only maternal death in the series was in a woman admitted in diabetic coma who developed anuria and at autopsy was found to have renal cortical necrosis. R.L.J.

Coates, John Robert; and Robbins, Jacob John (U.S. Naval Hosp., St. Albans, N.Y.): SEVERE HYPOGLYCEMIC SHOCK DUE TO CHLORPROPAMIDE. J.A.M.A. *170*:941-43, June 20, 1959.

An eighty-eight-year-old woman patient had received 250 mg. of chlorpropamide daily for two weeks as a substitute for insulin therapy. When the blood sugar level was found to be 220 mg. per 100 ml., the dosage was increased to 250 mg. twice daily. After one day, the patient was hospitalized in coma but was released from the emergency room after apparent complete recovery. On the next morning, she was again hospitalized in deep coma and the blood sugar level was 31 mg. per 100 ml. The next morning it was 8 mg. per 100 ml. Dramatic recovery was brought about by intravenous administration of dextrose and supplementary feedings. It would appear mandatory that patients receiving chlorpropamide be kept under close clinical observation, with frequent blood sugar level determinations.* B.F.K.

**Editor: To detect unsuspected or asymptomatic hypoglycemia due to prolonged action of hypoglycemic agents, blood sugar determinations in the postabsorptive state are most helpful.*

Cornblath, Marvin; Odell, Gerard B.; and Levin, Ephraim Y. (Harriet Lane Home of Johns Hopkins Hosp. and Pediat. of Sinai Hosp. and Johns Hopkins Univ. Sch. of Med., Baltimore, Md.): SYMPTOMATIC NEONATAL HYPOGLYCEMIA ASSOCIATED WITH TOXEMIA OF PREGNANCY. J. Pediat. 55:545-62, November 1959.

The authors describe in detail eight cases of symptomatic hypoglycemia in the neonatal period in infants born to toxemic mothers. Hypoglycemic symptoms included apnea, cyanosis, coma and convulsions. Some of the infants were found to be leucine-sensitive during the symptomatic period, but had a normal tolerance later on when symptoms had subsided. All infants responded to treatment with intravenous dextrose solutions for a brief period and became asymptomatic; however, three of the eight required cortisone or ACTH for brief periods of time to control hypoglycemia. Implications of the findings are discussed. R.L.J.

Corrêa, P. Riet; Marques, Maria; and Wagner, E. M. (Instituto de Fisiologia Exper. Faculdade de Medicina, Pôrto Alegre, Brazil): HYPERGLYCEMIA CAUSED BY THE ORAL ADMINISTRATION OF GLUCOSE IN TURTLES. Endocrinology 66:731-34, May 1960.

The oral administration of glucose to turtles resulted in transient hyperglycemia higher in winter than summer. Permanent diabetes was not produced. The islets of Langerhans were increased in number and size while beta cells showed degranulation and hydropic degeneration. Hyperglycemia disappeared and the pancreas returned to normal after cessation of glucose administration. H.L.W.

Dekaban, Anatole; Baird, Robert (National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Md.; Howard University Med. Sch., Washington, D.C.): THE OUTCOME OF PREGNANCY IN DIABETIC WOMEN. I. FETAL WASTAGE, MORTALITY, AND MORBIDITY IN THE OFFSPRING OF DIABETIC AND NORMAL CONTROL MOTHERS. J. Pediat. 55:563-76, November 1959.

The authors present a comparison of the outcomes of 235 pregnancies of diabetic women, some of the deliveries occurring in the prediabetic stage, with 249 pregnancies of matched normal controls. A comparison of fetal wastage, viz. neonatal deaths, stillbirths, and abortions, showed a higher percentage in the diabetic group, a finding which is consistent with previous studies. The fetal wastage during the prediabetic stage was somewhat less than that during the diabetic stage. Good control and early delivery had a favorable influence on the figures for fetal wastage, whereas the severity of the diabetes had no apparent effect. Of the 157 diabetic pregnancies, six produced abnormal surviving offspring, representing 3.8 per cent of the total pregnancies or 7.6 per cent of the surviving offspring, as compared to one abnormal surviving offspring in the normal controls, an incidence of 0.4 per cent, the difference being highly significant. R.L.J.

DeLawter, DeWitt E.; Moss, James M.; Tyroler, Sidney; and Canary, John J. (Georgetown University Med. Sch. and Diabetic Clin., Georgetown Univ. Hosp., Washington, D.C.): SECONDARY FAILURE OF RESPONSE TO TOLBUTAMIDE TREATMENT. J.A.M.A. *171*:1786-92, Nov. 28, 1959.

Two hundred nonketotic diabetic patients who received tolbutamide were followed up to three years. The average maintenance dose when patients were responding satisfactorily was 1 gm. per day. The dosage was raised to 3 gm. per day before the drug was considered to be ineffective. The primary failure rate, within the first year, was 16 per cent. The secondary rate of failure, after the first year, was 29.5 per cent. The monthly failure rate averaged about 3 per cent of the patients treated each month. Patients with poor and fair initial diabetic control develop secondary failure sooner than those with good and excellent control. Those over forty years of age with newly diagnosed diabetes, no previous treatment, slight obesity, minimal or no symptoms of diabetes and no history of acidosis, gave the most satisfactory response. Only two of the twenty-five patients given a retrial on tolbutamide therapy obtained a good response. A satisfactory response to treatment with chlorpropamide or metahexamide was obtained in 20 per cent of

the patients with secondary failure of response to tolbutamide. Phenethylbiguanide gave a satisfactory response in 55 per cent of these. There was no significant change in the insulin requirements of patients before treatment with tolbutamide and after their secondary failure of response to the drug. B.F.K.

Dodu, Silas R. A. (Korle Bu Hosp., Accra, Ghana): DIABETES AND HAEMOSIDEROSIS — HAEMOCHROMATOSIS — IN GHANA. Tr. Roy. Soc. Trop. Med. & Hyg. 52:425-30, September 1958.

Hemosiderosis is a frequent postmortem finding in certain parts of Africa; in Ghana, Edington reported an incidence of 40 per cent in 728 autopsies. The clinical significance of this prevalent condition is not known and the association of hemosiderosis with other diseases in Ghana may therefore be merely coincidental; however, among the forty-four diabetics included in the present investigation four were found to have hemosiderosis indistinguishable from idiopathic hemochromatosis.

These diabetics were investigated for the presence of hemosiderosis by section of aspirated sternal marrow, and seven were found to have heavy pigment deposits in the marrow. Liver biopsy was successful in six of the seven. Four (i.e., 9.1 per cent of the total investigated) were classified as hemochromatosis and one as early hemochromatosis. The remaining patient had iron pigment in the Kupffer cells only, in spite of heavy marrow siderosis. All four patients with established hemocromatosis were males aged between thirty-nine and fifty-six years. Biochemical tests of liver function and skin biopsy were of little help in diagnosis, but a large, hard liver and fairly severe diabetes with loss in weight were constant clinical findings.

It is concluded that hemosiderosis is not uncommon amongst diabetics in Ghana, and the combined malady of diabetes and advanced hemosiderosis is clinically and histopathologically indistinguishable from idiopathic hemochromatosis. W.R.K.

Donnell, George N.; Bergren, William R.; Bretthauer, Roger K.; and Hansen, R. G. (Children's Hosp., Los Angeles, Calif.; Sch. of Medicine, University of Southern California, Los Angeles; Dept. Agricultural Chem., Michigan State University, East Lansing, Mich.): THE ENZYMATIC EXPRESSION OF HETEROZYGOSITY IN FAMILIES OF CHILDREN WITH GALACTOSEMIA. Pediatrics 25:572-81, April 1960.

An enzymatic method for detection of the heterozygous carrier of the galactosemia gene is described. The method involves incubating a hemolysate of the subject's red cells with appropriate substrates, including UDPGlu, and measuring the amount of UDPGlu utilized and the amount of UDPGal formed. The heterozygote forms smaller amounts of UDPGal than normal, because of a partial deficiency of the enzyme Gal-1-P uridyl transferase. The homozygote has none of this enzyme and produces no UDPGal. This test was used in testing the families of children with galactosemia. All the parents tested showed the heterozygous condition. Three affected children of fourteen tested showed small amounts of activity. Eleven of seventeen siblings tested were heterozygous, in keeping with the predicted ratio. All normal controls showed adequate amount of activity. The test is shown to be an adequate method for detection of the heterozygous state. R.L.J.

Donovan, B. T.; and Jacobsohn, Dora (Inst. of Psychiatry, Denmark Hill, London S.E. 5, England; Inst. of Physiol., Univ. of Lund, Sweden): TESTOSTERONE AND THE GROWTH OF MAMMARY GLANDS AND OTHER TISSUES OF HYPOPHYSECTOMIZED RATS TREATED WITH THYROXINE, INSULIN AND CORTISONE. Acta endocrinol. 33:214-29, February 1960.

Growth of alveolar lobules in the mammary glands is produced in rats with intact pituitary glands after injections of testosterone but this does not occur after gonadectomy and hypophysectomy. The addition to therapy with testosterone of thyroxine and cortisone, of insulin and cortisone, or of thyroxine, insulin and cortisone did not correct this deficiency.

The last group, however, showed growth in length and weight even though not demonstrating the localized growth effect in the mammary glands. S.B.B.

Duncan, Garfield G. (Prof. of Med., University of Pennsylvania, and Dir. of the Med. Div. of the Pennsylvania Hosp. & the Benjamin Franklin Clinic, Philadelphia): PERSPECTIVES IN THE TREATMENT OF DIABETES. Am. J. M. Sc. 239:397-402, April 1960.

The author discusses the appropriate selection for the individual diabetic patient of the modality of treatment from the wide variety of diets, eight insulins and three oral agents now available. The goal is to so employ the therapies at hand that the patient receives full, rather than partial treatment of his disease with consequent well-being and retarded or nonprogressive degenerative changes.

For the overweight, who comprise 80 per cent of all diabetics by the author's estimate, there is recommended reduction of the total caloric intake sufficient to reduce the overweight. This measure alone is effective in controlling the diabetes, barring acute complications, of a majority of patients. Supplementation of the undernutrition program with a sulfonylurea compound is advised against because from the patient's viewpoint diet therapy then becomes secondary in importance to drug therapy, whereas attainment of success with diet alone gives this measure its proper significance. Drug therapy without weight loss is a treatment failure; there is no legitimate substitute for the reduction of the obese diabetic.

Approximately 10 per cent of diabetics are "ideal" candidates for sulfonylurea therapy. These patients are not overweight, have an adult-acquired, stable type of diabetes and are satisfactorily controlled in 75 per cent of instances with either chlorpropamide or tolbutamide, at times better than with insulin.

Phenformin is not a suitable substitute for sulfonylurea when these adequately regulate the diabetes; it causes anorexia, nausea and vomiting in 20 to 50 per cent of cases; its greatest promise lies in reducing the insulin requirement and in exerting a stabilizing effect on the juvenile type of diabetes.

Insulin in one form or another or in suitable combination and timing invariably is effective in lowering the blood sugar and is obligatory in about 10 per cent of patients, composed of the 5 per cent who are juveniles and of the 5 per cent of adults with a juvenile-type diabetes. Predictable results have been obtained with these plans of insulin therapy: (a) A single dose of an intermediate insulin (Globin, NPH or Lente) one hour before breakfast for the relatively mild patient. (b) A mixture of rapid-acting insulin (Crystalline or Semilente) with the intermediate insulin for the moderate patient in whom the latter alone fails to prevent hyperglycemia and glycosuria during the forenoon. (c) For the labile juvenile type diabetic, plan (b) is supplemented with an additional evening dose of intermediate insulin either at supper or bedtime.

For complications as severe infections or ketosis, Crystalline Insulin is administered every six hours around the clock. No class (c) patients as above defined have responded to oral

therapy without insulin but reductions in dosage and stabilization upon sulfonylureas have been reported. Sulfonylureas have occasionally been successful in class (b) patients.

The author advocates a liberal carbohydrate diet (up to 250 gm. per day or more), high in protein for diabetics of normal or under normal weight as a measure of lowering the fat quota of the diet. He expresses the conviction that the high fat proportion of diabetic diets in the past has contributed to the progression of atherosclerosis and feels the likelihood of benefit is sufficiently great to warrant extended clinical trial of low fat diets made up with highly unsaturated fats in angina and in diabetic retinopathy (20 gm. of fat per day). L.S.S.

Duncan, Leslie J. P.; and Baird, Joyce D. (Dept. Therapeutics, Univ. Edinburgh, Edinburgh, Scotland): COMPOUNDS ADMINISTERED ORALLY IN THE TREATMENT OF DIABETES MELLITUS. Pharmacol. Rev. *12*:91-158, March 1960.

Review paper with 451 references. J.A.

Egeli, Ekrem Serif; and Alp, Halûk (3rd Clinic of Internal Med., University of Istanbul, Turkey): EFFECT OF CARBUTAMIDE ON HEPATIC GLYCOGENOLYSIS ACTIVATED BY GLUCAGON: A STUDY USING HEPATIC-VEIN CATHETERISATION IN NONDIABETIC SUBJECTS. Lancet *1*:803-04, April 9, 1960.

The effect of carbutamide 3 gm. intravenously on hepatic glycogenolysis activated by glucagon was investigated in ten nondiabetic subjects by means of hepatic-vein catheterization.

The glycogenolytic action of glucagon was blocked by carbutamide, and this effect is probably related to the inhibition of hepatic enzymes. J.A.

Ellenberg, Max (Dept. of Med., The Mount Sinai Hosp., New York, N.Y.): DIABETIC NEUROPATHY: A CONSIDERATION OF FACTORS IN ONSET. Ann. Int. Med. *52*:1067-75, May 1960.

The author analyzed the clinical background of a large group of patients with diabetic neuropathy for factors of possible importance in pathogenesis. His data revealed the frequency of its occurrence in patients with good control, mild diabetes or undiagnosed diabetes. Its occurrence shortly after the initiation of good control by insulin or sulfonylurea drugs occurred after a period of time similar to that elapsing in patients who developed the disorder after a variety of stressful situations. Moreover, the course of the neuropathy was unchanged by continuation of the insulin or sulfonylurea therapy. S.B.B.

Elwood, J. C.; and Van Bruggen, J. T. (Dept. of Biochemistry, University of Oregon Med. School, Portland, Oreg.): LIPID METABOLISM IN THE DIABETIC RAT. III. ACETATE METABOLISM AND ACETOACETATE SYNTHESIS IN VITRO. J. Biol. Chem. *235*:568-72, March 1960.

Liver slices obtained from diabetic rats three to seven weeks after alloxan administration utilized less oxygen and produced less carbon dioxide than slices from control animals. Less CO_2 was formed from acetyl Co A but more $C^{14}O_2$ was formed from administered labeled acetate in the diabetic rats. Incorporation of acetate-1-C^{14} into fatty acids was decreased. Cholesterologenesis was depressed in the preparation from the diabetic rat, also the quantities of β-hydroxybutyrate and total ketone bodies formed. This is explained on the basis of decreased synthesis of acetoacetate because of limited supplies of acetyl Co A. A.R.C., JR.

Elwood, J. C.; Marcó, Alicia; and Van Bruggen, J. T. (Dept. of Biochemistry, University of Oregon Med. Sch., Portland, Oreg.): LIPID METABOLISM IN THE DIABETIC RAT. IV. METABOLISM OF ACETATE, ACETOACETATE, BUTYRATE, AND MEVALONATE IN VITRO. J. Biol. Chem. *235*:573-77, March 1960.

Labeled fat molecules were utilized to investigate the production of CO_2, fatty acid and cholesterol by rat liver slices. Cholesterol was labeled selectively by mevalonate-2-C^{14}. Acetoacetate appeared in lipid products preferentially. Butyrate failed to offer a pathway for fatty acid synthesis, but was converted to acetyl Co A. Defective hepatic lipid synthesis in the diabetic slices was demonstrated with both acetoacetate-3-C^{14} and butyrate-1-C^{14}. Cholesterologenesis was not disturbed in the diabetic animal beyond the stage of mevalonate participation. A.R.C., JR.

Estes, E. H., Jr.; Bogdonoff, M. D.; Friedberg, S. J.; Harlan, W. R., Jr.; and Trout, D. L. (Central Reference Lab., Veterans Administration Hosp. and the Dept. of Medicine, Duke University Medical Center, Durham, N.C.): THE EFFECT OF INSULIN ON NONESTERIFIED FATTY ACID RELEASE FROM THE HUMAN LEG. J. Clin. Invest. *38*:2131-34, December 1959.

The effect of injection of half to one unit of glucagon-free insulin into the femoral artery of six normal fasting human subjects showed a selective and immediate effect on the concentration of nonesterified fatty acids in the blood. A negative arteriovenous difference was observed which occurred within twenty minutes, and the effect on NEFA concentration was greater locally than in the other limb and elsewhere in the body. This confirms the local effectiveness of insulin by this route of injection and the participation of limb fat depots in the control of blood NEFA. S.B.B.

Etheridge, Charles L.; and Hines, Carl R. (Dept. of Medicine, Northwestern Univ. Med. Sch., Chicago, Ill.): PAINLESS PANCREATITIS WITH CHRONIC INSUFFICIENCY. Quart. Bull. Northwestern Univ. M. Sch. *33*:215-22, Fall 1959.

Two illustrative cases of painless pancreatitis are presented. One had steatorrhea while the other had symptoms (bleeding and bone pain) secondary to steatorrhea. Differential diagnosis is discussed.

Diagnosis of painless pancreatitis should be considered when: An adult develops diabetes mellitus though family history for that disease is lacking; or hypoprothrombinemia, severe osteomalacia, weight loss, or biliary tract obstruction of unknown cause is found.

The usefulness of the following diagnostic tests is stressed: X ray of the abdomen seeking evidence of pancreatic calcification, fecal fat excretion, bicarbonate content and volume of pancreatic secretion after secretin stimulation, absorption of isotopically labeled triolein, *d*-xylose tolerance test, and the glucose tolerance test. H.L.W.

Farquhar, Marilyn G.; Hopper, James, Jr.; and Moon, Henry D. (Depts. of Path. & Med., Univ. of California Sch. of Med., San Francisco): Am. J. Path. *35*:721-53, July-August 1959.

Seven patients with diabetes mellitus and varying degrees of renal involvement were studied. Both light and electron microscopy were employed in the examination of renal biopsy specimens.

Electron microscopy revealed an early thickening of the basement membrane, a finding not evident by light microscopy. Deposits of hyalin were found between adjacent endothelial cells. The hyalin resembled basement membrane in appearance and appeared at first as a diffuse lesion. Light microscopy showed

the lesion at first near the afferent arteriole and later in the more peripheral loops. As hyaline material accumulated the diffuse lesions developed into typical nodular lesions.

Fibrinoid deposits constituting the exudative lesion were found between the endothelial cells and the basement membrane. These lesions occurred in the more severely damaged kidneys.

The morphologic changes noted in the glomeruli of patients with diabetes could be differentiated from those changes occurring in disseminated lupus erythematosus, nephrosis, amyloidosis, pre-eclampsia, and eclampsia. H.L.W.

Fitch, Walter M.; and Chaikoff, I. L. (Dept. of Physiology, University of California, Berkeley): EXTENT AND PATTERNS OF ADAPTATION OF ENZYME ACTIVITIES IN LIVERS OF NORMAL RATS FED DIETS HIGH IN GLUCOSE AND FRUCTOSE. J. Biol. Chem. *235*:554-57, March 1960.

Rats were fed a 60 per cent glucose or fructose diet for seven days and assays performed for seventeen different liver enzymes which function in carbohydrate metabolism. The following enzymes increased in activity when the hexose-containing diet was substituted for the stock diet: phosphoglucose dehydrogenase and phosphogluconate dehydrogenase (hexose monophosphate oxidative pathway); phosphoglucomutase, α-glycerophosphate dehydrogenase, phosphoglyceraldehyde dehydrogenase, 3-phosphoglycerate kinase and lactate dehydrogenase (Embden-Meyerhof pathway); malate dehydrogenase (Krebs cycle); the transaminases, glutamate-aspartate and glutamate-alanine; and malate dehydrogenase. Certain enzymes were more active after fructose feeding than after glucose feeding: glucose 6-phosphatase, phosphogluconate dehydrogenase, aldolase, fructokinase and malate dehydrogenase. The data indicate that increasing the throughput in a metabolic pathway enhances the enzyme activity involved in the pathway. A.R.C., JR.

Gillmann, H.; and Sachsse, B. (I. & II. Dept. of Med., Medical Academy, Düsseldorf, Germany): STUDIES ON THE RELATIONSHIP BETWEEN MYOCARDIAL INFARCTION AND DIABETES MELLITUS. Deutsche med. Wchnschr. *84*:2070-72, Nov. 13, 1959.

The authors reviewed the histories of 659 consecutive hospital admissions with myocardial infarction. One hundred and seven of these patients were diabetics. The sex ratio of the nondiabetic patients was 76.6 per cent males against 23.4 per cent females; among the diabetics this ratio was 54.2/45.5 per cent. The average age at the time of the infarct was 60.5 for the nondiabetics (M 59.6, F 64.5) and 62.7 for the diabetics (M 61, F 64.8). Shock and circulatory failure were somewhat more frequent among the diabetics than the nondiabetics (54.3 per cent vs. 49.5 per cent), but the mortality rate for the first four weeks after the infarction was identical for both groups. The mortality seemed to depend primarily on the size of the infarct, and in the diabetics on the presence or absence of acidosis. The authors point out that neither the difference in the age distribution nor that of the sex distribution in their series has any specific significance for the correlation of myocardial infarction and diabetes mellitus. Careful statistical analysis seems to indicate that this difference is simply due to case selection since the incidence of diabetes is highest among people over the age of fifty and higher among women than men. Once a correction is made for age and sex comparable values are obtained for the nondiabetic and the diabetic population in regard to sex ratio, age at time of infarction and death rate due to infarction. The authors therefore do not subscribe to the concept that diabetes mellitus predisposes to myocardial occlusion. Unfortunately, no detailed data are given about the duration of the diabetes, its severity and complications, nor about the effect of the cardiac emergency on the diabetes. M.G.G.

Hall, James C.; Sordahl, Louis A.; and Stefko, Paul L. (Newark College of Arts and Sciences, Rutgers, The State University, Newark, N.J.): THE EFFECT OF INSULIN ON OXIDATIVE PHOSPHORYLATION IN NORMAL AND DIABETIC MITOCHONDRIA. J. Biol. Chem. *235*:1536-39, May 1960.

Liver mitochondria from alloxan-diabetic rats and depancreatized cats demonstrated a diminished ability to carry on oxidative phosphorylation. This was corrected by insulin, which permitted oxygen consumption and formation of adenosine triphosphate to return to normal. Mitochondria from diabetic animals were larger, more fragile and diminished in number as compared to those from normal animals. It is suggested that insulin may increase permeability by its effect on the mitochondria rather than on the cell. A.R.C., JR.

Hamwi, George J.; and Skillman, Thomas G. (Ohio State University Health Center, Columbus, Ohio): THE CLINICAL USEFULNESS OF ORALLY ADMINISTERED HYPOGLYCEMIC AGENTS. Postgrad. Med. *27*:687-95, June 1960.

This is a review of the oral hypoglycemic agents including the authors' personal views on their use. The potencies of the individual drugs were compared. The statistical incidence of toxicity in general use was compared with that of the authors' experience. The opinion was expressed that such toxicity may be modified by dosage or technic of administration. S.B.B.

Haworth, J. C.; and Coodin, Fischel J. (Dept. of Pediat., University of Manitoba, and the Children's Hosp., Winnipeg, Manitoba, Canada): IDIOPATHIC SPONTANEOUS HYPOGLYCEMIA IN CHILDREN: REPORT OF SEVEN CASES AND REVIEW OF THE LITERATURE. Pediatrics *25*:748-65, May 1960.

The authors describe their experiences with seven children with idiopathic spontaneous hypoglycemia. Case histories are presented for all children. The response to various types of therapy varied. One infant with onset at five and a half weeks responded poorly to steroids, ACTH, glucagon, adrenalin, and growth hormone, and died at nine months. She was not sensitive to leucine. Two children who did not respond to steroids had partial pancreatectomies. One was apparently cured while the other had no benefit. The pancreas of the child who responded well to pancreatectomy was normal, and that of the child who was not helped showed hyperplasia of islets. The variability in clinical course and response to therapy suggests that the condition is not a single clinical entity, but a group of conditions of varying etiology. The literature is reviewed and many references cited. R.L.J.

Jackson, Derrick; and Oakley, Wilfred (Diabetic Clinic, King's College Hosp., London S.E.5, England): CHLORPROPAMIDE IN THE TREATMENT OF DIABETES MELLITUS. Lancet *2*:752-54, Nov. 7, 1959.

Chlorpropamide was given to 126 diabetic patients, and in eighty-nine satisfactory diabetic control was produced.

Chlorpropamide has a greater range of activity than tolbutamide and is effective in cases which relapse on tolbutamide therapy. The incidence of toxic effects is low when the maximum dose does not exceed 375 mg. daily. The patient's age and the duration of diabetes had no bearing on the response to

chlorpropamide in this series.

Preliminary results suggest that steroid-induced diabetes can be suppressed by the administration of either tolbutamide or chlorpropamide in its early stages. J.A.

Knauff, H. G., and Böck, F. (From the II. Dept. of Med., University of Munich, Germany): THE EFFECT OF INSULIN HYPOGLYCEMIA ON THE FREE AMINO ACIDS AND THE ETHANOLAMIN OF THE BRAIN. Klin. Wchnschr. *38*:553-54, June 1, 1960.

The senior author had established in previous experiments that the spectrum of the free amino acids in the brain is relatively constant, and far less variable than the plasma content of free amino acids. This observation raised the question whether this stability of the free amino acids in the brain could be changed by altered metabolic conditions. Insulin hypoglycemia was chosen as an example. Nineteen rats were given 100 units insulin per kilogram body weight and decapitated five hours later; fifteen untreated rats were used as controls. A general decrease of most of the free cerebral amino acids was found. The decrease differed, however, between the various substances. Of the three amino acids which represent the bulk of the free cerebral amino acids, glutamic acid, glutamine and γ-amino-butyric acid, the first two decreased by an average of 30 per cent, while the third by not more than 15 per cent. On the other hand, a marked increase was found in the concentrations of ethanol-amine, phospho-ethylanolamine and serine, with the latter increasing by almost 100 per cent. The total amino-N content of the brain remained, however, about the same, which is explained by the fact that the decrease in one group of the amino acids is compensated by the increase in the other. The authors interpret their results as evidence that energy producing amino acids of the brain substances are utilized in the absence of glucose. The low molecular phosphoacids increase because they are the end product of the mobilization of brain substances. M.G.G.

KREBS CYCLE. Lancet *1*:907-09, April 23, 1960.

The Krebs Cycle is discussed in a leading article. Reference is made to the metabolic lesions and some of the enzyme poisons affecting the cycle. J.A.

Kurtz, Martin; Holtzman, Charles M.; and Meilman, Edward (The Long Island Jewish Hosp., New Hyde Park, Long Island, N.Y.): TOLBUTAMIDE HYPOGLYCEMIA IN ACUTELY DEPANCREATIZED DOGS. J. Clin. Invest. *38*:902-06, June 1959.

The authors investigated the effect of intravenously administered tolbutamide in preventing the rise in blood sugar values which occur promptly as a result of complete pancreatectomy in adult dogs. Tolbutamide did prevent the expected rise and its most decisive effect was at three to four hours. Delay in administration of tolbutamide for over one hour postoperatively decreased or abolished this effect.

The authors conclude that under the conditions of this experiment, tolbutamide did not require a pancreas in order to act but that the data do not exclude the need for insulin or insulin action to exert its effect. S.B.B.

Lawrence, A. M.; and Contopoulos, A. N. (Dept. of Anatomy, Univ. of California Sch. of Med. San Francisco 22, & Inst. of Experimental Biology, Univ. of Calif., Berkeley, Calif.): REPRODUCTIVE PERFORMANCE IN THE ALLOXAN DIABETIC FEMALE RAT. Acta endocrinol. *33*:175-84, February 1960.

This is a study of the anatomy and reproductive physiology of alloxan diabetic rats. Prepubertal female rats were rendered diabetic at thirty days of age and sacrificed after twenty days with blood sugar levels of 400-600 mg. per 100 ml. The weights of uteri and ovaries were strikingly less and their anatomy strikingly immature in the diabetic animals as compared with normals. This was so even when compared with a group of normals on diets restricted so that their weights were reduced to a degree similar to that of the diabetics. The same occurred forty-two days after the animals had been alloxanized at sixty days of age.

The rats were rendered diabetic at sixty days of age and allowed to go practically to term at twenty-one days without treatment and blood sugars of 225-500 mg. per 100 ml. Of nineteen animals with similar degrees of diabetes, twelve resorbed all their fetuses while seven produced 94 per cent viable, normal fetuses at term. No correlation was found between reproductive results and the blood sugar levels.

A study of lactational performance in eight diabetic animals showed a reduction in the diabetic animals. S.B.B.

Lazarus, Sydney S.; and Volk, Bruno W. (Isaac Albert Res. Inst. of Jewish Chronic Disease Hosp., Brooklyn, N.Y.): EFFECT OF DIABETOGENIC HORMONES ON BLOOD SUGAR AND PANCREAS OF SULFONYLUREA TREATED ANIMALS. Endocrinology *66*:702-11, May 1960.

Treatment of 50 per cent partially pancreatectomized dogs and of intact rabbits with tolbutamide or metahexamide did not affect the diabetogenic effectiveness of growth hormone or of cortisone. The sulfonylureas did not protect pancreatic beta cells from destruction by growth hormone nor did they enhance it. Pretreatment with sulfonylureas also failed to affect pancreatic changes due to diabetogenic hormones. H.L.W.

LeCompte, Philip M. (Dept. of Path., Faulkner Hosp. and Harvard Med. Sch., Boston): "INSULITIS" IN EARLY JUVENILE DIABETES. A.M.A. Arch. Path. *66*:450-57, October 1958.

The author describes four cases of "insulitis" in early juvenile diabetes. He examined the pancreas in microscopic detail in each case. He concluded that the cellular infiltration, usually lymphocytic, of the islands of Langerhans is a relatively rare but possibly significant lesion, encountered most often in diabetes of acute onset and short duration in children. Such cellular infiltration is commonly associated with the presence, in the islands in which it occurs, of cords or ribbons of cells with scanty cytoplasm and darkly stained nuclei, which are apparently α-cells and which probably are a manifestation of injury rather than of effective regeneration. This "insulitis" may in a few instances be a response to actual invasion of the islands by an infectious agent, although this has not been demonstrated. It is more likely the aftermath of an injury which may differ from those involved in the commonly recognized forms of experimental diabetes. It is probable that this injury in some way inhibits the regeneration of β-cells. E.A.W.

McCullagh, E. Perry (Dept. Endocrinology, Cleveland Clin., Cleveland): VASCULAR COMPLICATIONS OF DIABETES MELLITUS. Cleveland Clin. Quart. *26*:97-105, July 1959.

A good summary of the clinical and pathological manifestations and factors influencing the incidence and severity of vascular complications of diabetes mellitus is presented. The importance of careful treatment and earlier diagnosis of diabetes is stressed. The bibliography includes the most significant references on this important complication of diabetes. B.F.K.

Mahallawy, M. Nagy el; Sabour, Mohamed Sadek; Osman, Laila Mohamed; and Sadek, Samir Hanna (Abbassia Faculty of Medicine, Ein-Shams University, Cairo): METABOLIC AND ENDOCRINE ASPECTS OF DIABETIC NEPHROPATHY. Brit. M. J. *1*: 674-81, March 5, 1960.

Sixty-five diabetic patients were investigated to elucidate the endocrine and metabolic defects associated with diabetic nephropathy and to demonstrate by needle biopsy studies the pathogenic relationship of these defects to the development of the renal lesions.

Cases of diabetic nephropathy showed hypoalbuminemia, hyperglobulinemia, hypercholesterolemia in many instances, a rise in the protein-bound serum polysaccharides, hyponatremia, and hyperkalemia. The urine showed excessive amounts of 17-hydroxycorticosteroids and low values of 17-ketosteroids. Most patients with diabetic nephropathy could not retain the greater part of a test dose of vitamin B_{12} administered parenterally. J.A.

Margolin, Morris (University of Nebraska College of Medicine, Omaha): MANAGEMENT OF THE BLIND DIABETIC. Postgrad. Med. *26*:681-86, November 1959.

The author discussed the increasing importance of diabetes as a cause of blindness. From 1940 to 1957, in twenty states of the United States, there was a fivefold increase in the incidence of diabetes among the blind, and a sevenfold increase of blind diabetics.

He discussed the practical adjustments possible in the diabetic's handling of his disease, particularly in insulin administration and urine testing for sugar. Seven illustrative case reports were given. S.B.D.

O'Gorman, P.; Griffiths, P. D.; and Bloxam, Hazel R. (Dept. of Clinical Path. Guy's Hosp., London, England): ASCORBIC ACID INHIBITION OF THE GLUCOSE-OXIDASE TEST FOR GLYCOSURIA. Brit. M. J. *1*:603-06, Feb. 27, 1960.

Ascorbic acid levels above 10 mg./100 ml. in the urine will inhibit the glucose oxidase reaction and results in a negative test for glucosuria when Clinistix is used. However, levels of ascorbic acid inhibiting this test are not likely to occur on an average diet, but do occur in patients receiving therapeutic doses of the vitamin. The authors present a critical appraisal of Clinistix and Benedict tests for glucosuria in the light of the above results. J.A.

Politzer, W. M.; Hardegger, B.; and Schneider, T. (South African Inst. for Med. Res., Johannesburg; Seboche Hosp., Butha-Buthe, Basutoland: Diabetic Clinic, General Hosp., Johannesburg, Union of South Africa): INCIDENCE OF DIABETES MELLITUS IN THE BUTHA-BUTHE DISTRICT OF BASUTOLAND. Brit. M. J. *1*:615-17, Feb. 27, 1960.

In an examination of 3,000 Basuto in the Butha-Buthe area twelve cases of glycosuria were discovered. Seven of these cases were found to have blood-glucose levels above 140 mg. per 100 ml. —that is, 0.23 per cent of the cases examined. This figure is discussed in the light of a similar investigation in the United States of America, and points to a low incidence of diabetes mellitus in a primitive community. Stress is laid on the necessity for further studies among similar racial groups living under primitive and under more advanced conditions. J.A.

Pomeranze, Julius; Mouratoff, George T.; Gadek, Raymond J.; and King, Edward J. (New York Med. Coll., and Bird S. Coler Memorial Home and Hosp., New York): PHENETHYLBIGUANIDE, A NEW ORALLY GIVEN HYPOGLYCEMIC AGENT: REPORT AFTER TWO YEARS OF CLINICAL EXPERIENCE. J.A.M.A. *171*: 252-58, Sept. 19, 1959.

Over a two-year period 206 diabetic patients were treated with phenethylbiguanide (DBI) alone or together with insulin. They were unselected except for needing hypoglycemic therapy, and not because previous therapy had been unsuccessful. One hundred and ten patients were treated successfully with DBI alone. No evidence of secondary resistance to the drug has been encountered. Eighteen patients were successfully treated with DBI and a 50 per cent reduction in insulin dosage. Thirteen patients were later controlled with diet alone after careful supervision of diabetic management. One patient died from other causes, and five were unavailable for follow-up. In fifty-three patients, therapy was discontinued because of gastrointestinal symptoms. Many of these were in the earlier period of the study when overdosage was common. The careful low dose presentation, immediate limitation of dose ceiling with early symptoms and insistence of a liberal carbohydrate intake will lower the incidence of gastrointestinal symptoms. No organ toxicity has been observed in any patient maintained on this therapy for periods ranging to two years. B.F.K.

Rahmat-Ullah, Khalil Ahmed; and the late Bashir Ahmad (Pakistan Council of Scientific and Industrial Res., Lahore, West Pakistan): INSULIN CONTENT OF PANCREAS FROM LAHORE SLAUGHTER HOUSES. J. Sci. Ind. Res. *1*:73-75, January 1958.

A number of extracts were prepared from beef and mutton pancreas and assayed. The insulin content of beef pancreas ranged from 892-1,002 units per kilogram and that of mutton pancreas from 585-695 units per kilogram. These yields are much lower than those reported in the literature for the pancreas of normal animals of these species.

It has been estimated that the slaughter houses of Lahore which provide about 30-40 kg. weight of the pancreas per day can yield about 30,000 units of insulin per day. This figure is too low to justify the production of insulin on a commercial basis. However, since the total number of animals slaughtered in the country in different slaughter houses is very large, there still remains the possibility that if the slaughter houses are scientifically organized, and freezing facilities provided, the production of insulin and even of other glandular products may come within the range of feasibility. W.R.K.

Rogers, Frank A. (Dept. of Surgery, Coll. of Med. Evangelists, Sch. of Medicine, Los Angeles, Calif.): ISLET CELL TUMORS OF THE PANCREAS AND HYPERINSULINISM. Am. J. Surg. *99*: 268-82, March 1960.

The causes of spontaneous hypoglycemia are outlined. Data are summarized regarding seventeen cases of islet cell tumors treated at the Los Angeles County General Hospital. Blood glucose is usually less than 50 mg. per 100 ml. and symptoms are severe, recurrent, precipitated by fasting and relieved by glucose. Adrenal or pituitary insufficiency, central nervous disease, gastric surgery, metastatic carcinoma and severe liver disease must be ruled out. Subtotal or total pancreatectomy is performed when adenoma is not found. Surgery is justified because of potential damage to the nervous system from hypoglycemia and also the high incidence of malignancy (10 per cent). A.R.C., JR.

Schrade, W.; Bohle, E.; Biegler, R.; Meder, V.; and Teicke, R. (From I. Dept. of Med., Univ. of Frankfurt/Main, Germany):

GASCHROMATOGRAPHIC STUDIES ON THE SERUM FATTY ACIDS IN MAN. *I.* ON THE DISTRIBUTION OF THE FATTY ACIDS IN THE SERUM IN HEALTH, IN ARTERIOSCLEROSIS AND IN DIABETES. Klin. Wchnschr. *38*:126-34, Feb. 1, 1960.

The methyl esters of the total serum lipids of twenty-five healthy individuals, twenty-six arteriosclerotics with hyperlipemia, seven arteriosclerotics with normolipemia, fourteen diabetics with and eight without hyperlipemia were analyzed by gas chromatography. In the sera of healthy subjects the following partition was found: 0.28 per cent laurinic acid, 1.49 per cent myristinic acid, 27.45 per cent palmitinic acid, 6.63 per cent stearinic acid, 6.82 per cent palmitoleinic acid, 25.34 per cent oleic acid, 23.98 per cent linoleic acid, 0.76 per cent linolenic acid and 4.27 per cent arachidonic acid. In the sera of hyperlipemic arteriosclerotic subjects there was an increase of the palmitinic acid to 32.15 per cent, of the palmitoleinic acid to 8.83 per cent and of the oleic acid to 27.45 per cent. The stearinic acid content was unchanged and the linoleic and arachidonic acids were decreased. In the normolipemic arteriosclerotic sera, smaller similar changes were observed which were not significant statistically. The normolipemic diabetic sera did not show any differences from the normal control sera, but the hyperlipemic diabetic sera contained markedly elevated levels of palmitinic (33.48 per cent) and oleic acid (28.49 per cent), and lower amounts of linoleic (18.64 per cent) and arachidonic acids (2.45 per cent). These differences in the partition of the fatty acids between the normolipemic and hyperlipemic sera of diabetic subjects were found to be statistically significant. The differences between the hyperlipemic sera of arteriosclerotic and of diabetic subjects had, however, no statistical significance. M.G.G.

Segal, Harold L.; and Washko, Mary E. (Biochemistry Dept., Univ. of Pittsburgh Sch. of Med., Pittsburgh, Penn.): STUDIES OF LIVER GLUCOSE 6-PHOSPHATASE. III. SOLUBILIZATION AND PROPERTIES OF THE ENZYME FROM NORMAL AND DIABETIC RATS. J. Biol. Chem. *234*:1937-41, August 1959.

Glucose 6-phosphatase was elevated in liver homogenates by production of alloxan diabetes in rats. Treatment of the animals with Protamine Zinc Insulin for two to three days reduced the enzyme level to normal, but administration of hydrocortisone or cortisone had little or no effect. Preparations containing isolated, washed microsomes exhibited the same alterations as the homogenates. If the microsomes were disrupted, the Michaelis constants of diabetic and normal enzymes became equal. The presence of a competitive inhibitor in the microsomes of diabetic liver is postulated to explain these results. A.R.C., JR.

Shoemaker, William C.; Van Itallie, Theodore B. (Harvard Med. Sch., Boston, Mass. & Michael Reese Hosp., Chicago, Ill.): THE HEPATIC RESPONSE TO GLUCAGON IN THE UNANESTHETIZED DOG. Endocrinology 66:260-68, February 1960.

Crystalline glucagon .02 mg./kg. was injected intravenously in unanesthetized dogs. Plastic catheters had previously been implanted in the left common hepatic vein, the portal vein and the splenic artery. The injection of glucagon produced an increase in hepatic blood flow and hepatic glucose output, the latter approximating half of the liver glycogen.

Fasting with resultant liver glycogen depletion caused a decline in both the hepatic blood flow and hepatic glucose output response to glucagon. The liver took up an increased amount of alpha amino nitrogen after administration of glucagon. This finding suggested increased gluconeogenesis to compensate for hepatic glycogen depletion. H.L.W.

Skaug, O. E.; and Lingjærde, P. (Res. Lab., Lier Hosp., Lier, Norway): THE EFFECT OF INSULIN ON BLOOD SUGAR, ELECTROLYTES, PLASMA 17-HYDROXYCORTICOSTEROIDS, AND CIRCULATING EOSINOPHILS IN ADULT WOMEN. Scandinav. J. Clin. & Lab. Invest. *12*:71-75, 1960.

Insulin in a dose of 0.1 I.U. per kilogram body weight was administered intravenously to fourteen adult women. Blood sugar fell to 40 per cent of fasting value in thirty minutes; initial level was restored in 120 minutes. The anthrone method for blood sugar determinations give insignificantly lower values than the original Hagedorn-Jensen method, but the curves after insulin are identical. Serum inorganic phosphate fell to 62 per cent in thirty minutes, and reached initial level in about 180 minutes. Serum potassium fell to 80 per cent in thirty minutes; initial level was restored in about 150 minutes. Plasma 17-hydroxycorticosteroids fell slightly in thirty minutes, rose to 125 per cent in sixty minutes and fell to 68 per cent of initial value in 180 minutes. Blood eosinophils rose to 160 per cent in thirty minutes, and fell to 57 per cent of initial value in 180 minutes. W.R.K.

Wong, Rose K. L.; and Van Bruggen, J. T. (Dept. of Biochemistry, Univ. of Oregon Med. Sch., Portland, Oreg.): LIPID METABOLISM IN THE DIABETIC RAT. II. CHOLESTEROL TURNOVER STUDIES. J. Biol. Chem. *235*:30-33, January 1960.

An impairment in the degradation of cholesterol by rat liver was demonstrated after alloxan or pancreatectomy diabetes. Cholesterol turnover in carcass, skin, gut, liver and serum measured by acetate-1-C^{14} was similar in the two diabetic preparations. A.R.C., JR.

Wyshak, Grace; Snegireff, Leonid S.; and Law, Augusta F. (Harvard Univ. School of Public Health, Dept. of Public Health Practice, Gerontology, and Chronic Disease Unit, Boston, Mass.): WORK EXPERIENCE OF PERSONS WITH CARDIOVASCULAR DISEASE OR DIABETES. J. Chron. Dis. *10*:525-37, December 1959.

This was a study of the work record of 691 persons with heart disease or diabetes, and an equal, matched control group in industry. The workers were engaged in a wide cross section of occupations in seventeen firms, both industrial and service activities.

Although there was greater absenteeism among those with diabetes and heart disease, it was less than expected. The disability rate was greater among young rheumatics and less among the older group and those in sedentary positions.

Analysis of both the industrial medical services offered and received indicated that company medical services contributed to absentee prevention However, of even greater importance was the proper job placement of such individuals. S.B.B.

ORGANIZATION SECTION

OFFICERS AND MEMBERS OF COUNCIL, AMERICAN DIABETES ASSOCIATION, 1960-1961

HONORARY PRESIDENTS, ELLIOTT P. JOSLIN, M.D., *Boston*; CHARLES H. BEST, M.D., *Toronto*

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TERM EXPIRING 1962

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ARNOLD LAZAROW, M.D., *Minneapolis*
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TERM EXPIRING 1963

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WILLIAM H. GRISHAW, M.D., *Beverly Hills*
GEORGE J. HAMWI, M.D., *Columbus, Ohio*
HENRY E. MARKS, M.D., *New York*
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PRISCILLA WHITE, M.D., *Boston*

PAST PRESIDENTS

JOHN A. REED, M.D., *Washington, D.C.*
ALEXANDER MARBLE, M.D., *Boston;* FRANCIS D. W. LUKENS, M.D., *Philadelphia*

EX OFFICIO

JOSEPH L. IZZO, M.D., *Rochester, New York,* Chairman, Board of State Governors
MAURICE PROTAS, M.D., *Washington, D.C.,* Chairman, Assembly of Delegates

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Twentieth Annual Meeting

The Twentieth Annual Meeting of the American Diabetes Association was held at the Deauville Hotel in Miami Beach, Florida, June 11-12. Names of Officers and Councilors elected for the 1960-61 organizational year, as announced in the July-August DIABETES, are listed on the above masthead.

SCIENTIFIC SESSIONS

Five Scientific Sessions, instead of the usual three, were held this year: Saturday morning and afternoon Sessions on June 11, two concurrent Sunday morning Sessions—one experimental and one clinical—and a final Session on Sunday afternoon, June 12. In all, forty-one papers were presented, and twenty-one others were included by abstract in the printed program.

The Committee on Scientific Programs, under the Chairmanship of Blair Holcomb, M.D., included the following members: Franklin B. Peck, Sr., M.D., Vice Chairman; James Ashmore, Ph.D.; Thaddeus S. Danowski, M.D.; Irving Graef, M.D.; and Harvey C. Knowles, Jr., M.D.

The Banting Memorial Lecture was delivered by Priscilla White, M.D., Assistant Professor of Pediatrics at Tufts University Medical School, and affiliated with the New England Deaconess Hospital, Faulkner Hospital, Boston Lying-in Hospital, Boston Floating Hospital, and the New England Hospital. The first woman to deliver this honorary lecture, Dr. White spoke on "Childhood Diabetes—Its Course, and Influence upon the Second and Third Generations." Her paper appears on pages 345-55 of this issue of DIABETES.

Albert E. Renold, M.D., recipient of the 1960 Lilly Award, presented a paper titled "The Use of Adipose Tissue for the Measurement of Insulin-like Activity: Problems and Progress Report."

A summary report of a special conference on diabetic retinopathy held in Haddonfield, New Jersey, May 1-2, by the National Institute of Neurological Diseases and Blindness was presented by the Conference Chairman, Irving H. Leopold, M.D., Chairman, Department of Ophthalmology, University of Pennsylvania Graduate School of Medicine.

SPECIAL SESSIONS

The Board of State Governors held a meeting at which members of the Council were guests.

The Assembly of Delegates convened on Saturday and Sunday, June 11-12, with Maurice Protas, M.D., Chairman, presiding.

The Special Program on Saturday morning included the following:

- Panel discussions on "Employment of Diabetics," "Camps for Diabetic Children," and "Public Exhibits and Displays for County and Health Fairs."
- "Methods of Diet Education," by Deaconess Maude Behrman, Director of Mercer Memorial House, Atlantic City, and Consulting Dietitian of ADA FORECAST.
- "Life Insurance for Diabetics," by Paul S. Entmacher, M.D., Assistant Medical Director, Metropolitan Life Insurance Company, New York City.

The Annual Session on Saturday afternoon included the Open-

ing of the Assembly, by Dr. Protas; Address by the President, Francis D. W. Lukens, M.D.; Minutes of Previous Session June 4, 1959, by Mrs. Enos F. Kraschel, Secretary; Remarks by Louis C. Bernst, Advisor for Affiliate Associations; Reports on Activities of Committees of the American Diabetes Association by their Chairmen: Committee on Affiliate Associations, by Alexander Marble, M.D., Boston; Committee on Camps, by James B. Hurd, M.D., Chicago; Committee on Employment, by William H. Grishaw, M.D., Los Angeles, for Joseph T. Beardwood, Jr., M.D., Philadelphia; Committee on Information for Diabetics, by Dr. Grishaw; Committee on Public Education and Detection, by Louis K. Alpert, M.D., Washington, D.C.; Committee on Research and Fellowships, by Jerome W. Conn, M.D., Ann Arbor.

At this session, Dr. Protas and Mrs. Kraschel were re-elected Chairman and Secretary respectively.

On Sunday, June 12, a diet exhibit by Deaconess Behrman and a Workshop for Administrative Personnel of Affiliate Associations were held. Films were shown from 2-5 p.m., entitled: "The Discoverers," "The Man Who Beat Death," "The Medicine Man," "Diabetes and You, Too," "Carol Haney—Patient Education Film," and "TV Spot Announcements for Diabetes Detection Drive."

ANNUAL BANQUET

The Banquet was held on Saturday evening, June 11. Invocation was offered by Deaconess Behrman. The Annual Address of the President was then delivered by Francis D. W. Lukens, M.D., Philadelphia:

YOUR VARIOUS OPINIONS

FRANCIS D. W. LUKENS, M.D., PHILADELPHIA

Every member of this Association knows that we are suffering from growing pains. The syndrome, not yet in the textbooks, consists of Councilors' headaches, spastic stasis of committees, laudable restlessness of many individual members and miscellaneous forms of Affiliate itching. The treatment consists of decalcification, reorganization, representation and mental catharsis, all directed to achieve a clear definition of the purposes and directions of our future activities. It is a gladsome fact that on our twentieth anniversary, I should mention growth as our principal problem. Would any of you wish it otherwise?

To seek your opinions on some of the matters confronting your Association, the Council approved of my sending a questionnaire to the membership. In round figures, 2,500 questionnaires were mailed and 850 answers received. This 34 per cent reply affords a useful sampling of your various opinions, and provides an index of interest in the ADA which is most encouraging. First of all, then, I thank you for your response.

This is not the time to labor over the statistics of the questionnaire. I shall mention parts of a few questions and then note some of the comments which you made.

The first question was: "Are you in accord with the present program of the American Diabetes Association?" I cite this question to indicate certain psychological difficulties and the care needed in interpreting the answers. A person who answered "Yes" might agree with the stated purposes of the program, yet have serious reservations about how well we were fulfilling these objectives. Another who answered "No" might be thinking only of our non-Utopian progress and yet might approve of our goals. With this warning, I should note that seventy-six marked "No" to this question, but when added comment was provided, it expressed the desire for change in the emphasis on our fourfold program which was never branded as wrong.

FRANCIS D. W. LUKENS, M.D., PRESIDENT, 1959-60

Another example of the problem of interpretation is seen when Question 2 is considered. Question 2 was: "Are you in accord with the present organizational structure of the ADA?" One hundred and thirty-four answered "No." Of these, 55 per cent voted that we should become solely a professional organization, and 34 per cent voted against becoming only professional. It is clear that the answer "No" can be given for widely different reasons.

Questions 3 and 4 concerning professional versus health

agency activity and the matter of fund raising were in a sense repetitious. This double questioning had been set up deliberately in the hope of evoking as much comment as possible on these key problems which confront your Association. To 3a, "Should we become solely medical?" 345 replied, whereas to 4a, "Do you favor public fund raising by the ADA?" 745 replied. I do not understand this difference and hope you will discuss these questions among yourselves and with the Councilors. Finally, of the 745 who voted on national public fund raising, 495 voted "No," 260 voted "Yes," and the ninety-five who did not vote make up the full 850.

But after all, fund raising is a means to an end and the first problem is to ascertain the ends to which we shall devote ourselves. For this, one seeks more than the "Yes" or "No" votes, but before I leave such votes, may I mention that they add important breadth to any conclusion derived from your personal comments? Now, I report one of the best features of this undertaking, namely, the large number of added comments. Three hundred and ninety-four or 46 per cent of the 850 replies had some added remarks.

These remarks covered a wide range of topics. Many pertained to professional education and have been transmitted to Dr. Danowski and his committee. Some concerned the Journal and I have presented them to the Editorial Board this week Here I shall focus on your comments about our organization and purposes, which lead me to the following thoughts:

There were several remarks critical of the Council, not as individuals but as an unrepresentative or undemocratic form of government. My own thoughts after your prodding are these: A Council is probably the best form of government for a group which is small, professional and held together by a common intellectual interest. This means a group for which money, power and controversy about policy are essentially unimportant. This was the case when the ADA was founded. With an enlarged membership and with the growth of widespread and varied local interest in diabetes, this may no longer be the case. It *is* no longer the case if you wish to change things to, let us say, a larger assembly of locally elected representatives. There are provisions for changing the Bylaws or Constitution.

Another problem, emphasized by your votes and your comments, is the weight to be given to the several components of our four-point program. Here is the nub of the whole matter of policy. In general, your opinions differ widely about how much we should concentrate on professional activities and how much we should expand into public activities. In view of the many and vigorous statements you have submitted, you will have to face the following alternatives, which were outlined by Dr. Marble last year. To make them clear, I shall exaggerate but I doubt if much compromise should be considered. Won't our decisions be better if facts are faced first and if modifications come later?

1. We can become a solely medical organization, terminate the Affiliate system as legal units of our Association which are at present subject to our regulation. One assumes that the members of the ADA would support their local independent units and aid in local fund raising, detection, public education, etc. Under such a plan, the local groups would have complete autonomy, which many comments requested.

2. We can become a full-scale national voluntary health agency, with the hazards of this venture. The majority, if not all of our professional activities, could probably be retained under this structure.

3. We can deliberately foster the development of two national organizations, one for professional activities and another for voluntary health functions, fund raising, etc.

Thus far I have mentioned two problems that confront us, namely, our government and the decisions about our future program. When put together in this fashion, it seems logical to suggest that our own government or organization be altered in the direction of broader representation and that the improved organization make the decisions about its program. Once again, the reasons for this should be clear. Our growth in size and in the variety of our activities suggests that a corresponding growth in the part played by our membership is in order. This in turn should lead to more discussion, better education of the members about the ADA and ultimately to a wiser decision about what you, the Association, want to do next.

These thoughts have been discussed with your Committee on Policies which I may announce has this week presented to the Council recommendations for broadening the base of government of the Association. Their proposals include an extensive revision of the Bylaws. This will provide for (1) an enlarged Nominating Committee of the ADA composed of the three immediate Past Presidents of the Association plus the Chairman and Vice Chairman of the Assembly of Delegates. (2) For the first time since their organization ten or more years ago, the Affiliates will be recognized by our Bylaws. (3) There will be a class of Affiliate Members. These will be voting and/or dues-paying physician members of Affiliates who are not Active Members of the American Diabetes Association. (4) The Council will be enlarged by five additional members nominated and elected by the Assembly of Delegates. These items from the three to four pages of proposed revision of the Bylaws should indicate the interest of the ADA in improving the representation of its members and of their associates in the local Affiliates. Details will have to be reduced to writing but the spirit of this action should be manifest. I may further note that the Council has approved of these recommendations in principle and ordered them implemented.

In the welter of your various opinions and in the proper search for organizational growth and improvement, let us not forget the ABC's of our own history. We have come to this point because for twenty years many devoted people have worked for the cause of the diabetic, albeit in their varied individual fashions. Let us not forget this as we talk of organization and policy. Some years ago, Dr. Ricketts addressed you under the title, "Where, oh where will the money come from?" Remember that administration, government, organization, and even money accomplish nothing of themselves. At best they smooth the path for people and as long as we have an interest in diabetes we will be, in Biblical words, seeking "laborers for the vineyard." We have had loyal and active workers in these first twenty years. I pay them all my personal tribute on this twentieth anniversary and I ask you never to cease asking this paraphrase of Dr. Ricketts' question: "Where, oh where, will the labor come from?" If our present enthusiasm matches that of our charter members, the future course of the American Diabetes Association will be one of continuing progress.

The Banting Medal

The Banting Medal was presented by Dr. Lukens, retiring President, to Priscilla White, M.D., Banting Memorial Lecturer, and to J. B. Collip, Ph.D., M.D., D.Sc., Dean of Medicine, Faculty of Medicine, The University of Western Ontario, London, Ontario, Canada. Dr. Collip received the Medal for collaboration with Dr. Frederick G. Banting and Dr. Charles H. Best in obtaining enzyme-free, nontoxic insulin from the pancreas of cattle, and "for a lifetime of research and the direction of research." A Banting Medal was also presented to Dr. Lukens, retiring President, by Alexander Marble, M.D., immediate past President, for his services during the past year as President of the ADA.

Banquet Highlights

- Miss Edith Jenkins was presented the 1960 "Citation as an Outstanding Layman." Miss Jenkins, a founder and former President of the Lay Society of The Indianapolis Diabetes Association (1954-56), previously served in the offices of First Vice President and Second Vice President. In 1954 she originated the Society's *Bulletin*. For the past six years, she headed the Lay Society's participation in the annual Diabetes Detection Drive. The award was made by Maurice Protas, M.D., Washington, D.C., Chairman of the Assembly of Delegates of the ADA.
- Frederick W. Williams, M.D., New York, was presented with a scroll, designed and encased in a handmade frame by Blair Holcomb, M.D., Portland, Oregon, in gratitude for his long and faithful service as Editor in Chief of the ADA FORECAST.
- Mr. J. Richard Connelly, New York, Executive Director, was presented a certificate of appreciation by Dr. Lukens signed by each member of the Council.
- Dr. Warren J. Wisby, Associate Professor of Marine Biology, The Marine Laboratory, University of Miami, Miami, Florida, was special speaker of the evening. His topic was "Social Behavior in Fishes."

Banting Medals were awarded at the Twentieth Annual Meeting to Priscilla White, M.D.; J. B. Collip, Ph.D., M.D., D.Sc.; and to Francis D. W. Lukens, M.D., retiring President.

The Lilly Award

After the address of the President, the 1960 Lilly Award, consisting of $1,000 and a medal, was presented to Albert E. Renold, M.D., Boston, for his work on the delayed or adaptive effect of insulin on the liver, his investigation of the metabolism of fructose and sorbitol in normal and diabetic subjects, and on the metabolism of adipose tissue. The recipient of this annual Award is chosen by the ADA Committee on Scientific Awards from investigators under forty years of age who have been nominated by members of the Association. It is made to recognize "demonstrated research in the field of diabetes, taking into consideration independence of thought and originality." Dr. Renold is author or co-author of ninety-three scientific papers. He is Assistant Professor of Medicine, Harvard Medical School, Director of the Baker Clinic Research Laboratory, New England Deaconess Hospital, and an Associate in Medicine (Biochemistry) at the Peter Bent Brigham Hospital.

ALBERT E. RENOLD, M.D.

Honorable Mention in the 1960 Lilly Award contest was given to Rosalyn S. Yalow, Ph.D., for her studies on the assay of insulin in blood by an immunological method. Dr. Yalow is Assistant Chief, Radioisotope Service, Veterans Administration Hospital, Bronx, New York. She is the first to receive Honorable Mention in this Award contest.

ANNUAL BUSINESS MEETING

The Annual Business Meeting of the American Diabetes Association was held Sunday, June 12, at 12:10 p.m. Francis D. W. Lukens, M.D., presided. Reports by the Secretary, Treasurer, Executive Director and Nominating Committee were followed by Installation of Incoming President, and Remarks of the Newly-installed President.

Report of the Secretary

Mr. President, and members of the Association. As your Secretary, I am very pleased to report that the Association is doing a tremendous job in the field of diabetes.

The Twenty-first Annual Meeting will be held at the Commodore Hotel in New York City, June 24-25, 1961; and the Twenty-second Annual Meeting will be held at the Conrad Hilton Hotel in Chicago, June 9-10, 1962.

The Ninth Postgraduate Course will be held Jan. 18, 19 and 20, 1961, in New Orleans. The Detroit-Ann Arbor area has been selected as the place for the Tenth Postgraduate Course in January 1962.

A new scientific exhibit entitled "Everyday Problems in Diabetes: 201 Crystal-clear Answers" will be displayed at the American Medical Association Meeting, June 13-17, Booth No. 326, Scientific Exhibit Section, Miami Beach Auditorium and Exhibition Hall, and it is hoped that everyone will visit it. The exhibit was developed by the Committee on Scientific Exhibits, chaired by Dr. Marshall I. Hewitt, in collaboration with the Steering Committee of the Committee on Professional Education, chaired by Dr. T. S. Danowski.

Our Research Fellowship program is progressing, and the following Fellowships have been awarded for the 1960-61 academic year:

David Norman, Ph.D., California Institute of Technology, will complete the third and final year of the Adler Foundation Research Fellowship.

Bruce M. Carruthers, M.D., Department of Medicine, Hospital of the University of Pennsylvania, will continue his work with Francis C. Wood, M.D.

Jurgen Steinke, M.D., Baker Clinic Research Laboratory, Department of Medicine, Harvard University Medical School, will continue his work with George W. Thorn, M.D., and Albert E. Renold, M.D.

John A. Colwell, M.D., Department of Medicine, Northwestern University Medical School, to work with Arthur R. Colwell, Sr., M.D.

Jack Kane Goldman, M.D., Harvard University School of Medicine, to work with George W. Thorn, M.D., and Albert E. Renold, M.D.

The Committee on Scientific Awards has selected J. William Allgood, of the Medical College of South Carolina, as the winner of the $250 award provided by the St. Louis Diabetes Association, for the best paper in the 1959-60 Graduate and Medical Student-Intern Essay Contest reporting original work. The title of his paper is "The Renal Clearance of I^{131} during the Infusion of NaI^{131} and Insulin-I^{131}." Honorable mention is being given to the following: Joseph R. Williamson, M.D., of Washington University School of Medicine, for his paper entitled "Electron Microscopy of Glycogenic Changes in Beta Cells in Experimental Diabetes"; and to Ann Lawrence, of the University of California School of Medicine, for her paper entitled "Studies in Reproductive Physiology in the Alloxan Diabetic Female Rat: The Endocrine Basis for Impairment of Reproductive Function in Diabetes Mellitus."

The $100 prize for the best review article or case report has been awarded to Phyllis Grant, of Kansas University Medical Center, for her paper entitled "The Role of Potassium in the Therapy of Diabetic Acidosis." Honorable mention in this prize category is being given to Lonnie Hanauer, A.B., and Jack M. Batson, M.D., of Cornell University Medical College and New York Hospital, respectively, for their paper entitled "Anaphylactic Shock Following Insulin Injection: Case Report and Review of the Literature."

The total membership of our Association is now 2,575 with eleven new applications pending.

ADA FORECAST continues to be a most unique service in the field of patient education, and its subscribers now number approximately 50,000.

We suffered a great loss this year with the death of Dr. William C. Stadie, Editor of DIABETES. However, as you know, Dr. Irving Graef, who formerly served as Associate Editor, has been appointed Editor, and Dr. Francis D. W. Lukens has been named Chairman of the Editorial Board of the Journal.

In addition to Dr. Stadie, we also have had the loss of three eminent Past Presidents—Drs. Edward S. Dillon, Lester J. Palmer, and Russell M. Wilder.

Time does not permit a report of the activities of all of the various committees and boards dealing with the aims and objectives of the Association. The organizational activity this year was at an all-time high. This has been a productive and informative meeting, and in addition to the many activities currently in progress, a number of new projects have been authorized.

On behalf of the membership, I wish to express our appreciation to Mr. Connelly and his staff for the management of our work in the field of diabetes.

E. PAUL SHERIDAN, M.D.

(In addition, Dr. Sheridan read a letter from Prof. F. G. Young, Chairman of the newly formed Medical and Scientific Section of The British Diabetic Association, extending an invitation to members of the American Diabetes Association to attend meetings of the Section. Please see page 440 for further details.)

Report of the Treasurer

The American Diabetes Association completed the fiscal year ending March 31, 1960, with an excess of income over operating expenses (exclusive of Government Grants and Bequests) of $24,000.

Total operating income for the year amounted to $465,000 and program expenses were $441,000. In addition, $392,000 was received from Bequests, $360,000 of which was earmarked for research. Sixty-five thousand dollars was received from the National Institutes of Health in support of Grants for the Diabetes Program Directors' Workshop and the Comprehensive Survey of Diabetes Abstracts Coverage in the amounts of $22,500 and $42,600 respectively. Including the aforementioned Bequests and Government Grants totaling $457,000 and deducting expenditures applicable to the Grants ($26,000), our income from all sources exceeds expenses by $455,000.

Income from contributions is about $186,000 or 40 per cent of our total operating income with $172,000 of this amount deposited to the General Fund and $14,000 restricted to research. Affiliate Associations contributed a total of $7,432, Sus-

taining Corporate Members a total of $137,500, nonmember corporations $6,148, Foundations a total of $13,400, ADA FORECAST readers $10,905, and the balance was received from in memoriam gifts and donations from clubs, members, etc.

As mentioned previously, 40 per cent of our total operating income was from contributions; 60 per cent or about $279,000 was earned income. This represents items such as membership dues, $15,800; DIABETES Journal subscriptions, $53,100; ADA FORECAST subscriptions, $101,500; sales of testing material, publications, interest on savings, interest and dividends on investments and miscellaneous amount to $99,600. The Eighth Postgraduate Course added another $9,000.

Of the aforementioned $441,000 of expenses, distribution by Funds was as follows: Professional Education represented 28 per cent of our total expenses or about $122,900. Patient Education amounted to 37 per cent of our total expenses or $162,000, Public Education and Case Finding $96,000 (22 per cent) and Research and Fellowships, $22,250 or 5 per cent.

In summarization, the American Diabetes Association is in a sound financial position. Our operating capital is adequate to meet current obligations, reserve funds in savings banks are sufficient to insure more than a year's operation in the event of an emergency, research funds are steadily accumulating and all indications point to continued but not necessarily increasing financial support from contributors and income producing activities.

THOMAS P. SHARKEY, M.D.

Remark by Cecil Striker, M.D.

Mr. President, I would like to point out that twenty years ago this month we were paying my secretary $35 a month to take care of the correspondence of the American Diabetes Association.

Report of the Executive Director

Dr. Lukens, Officers and members of the American Diabetes Association: This past year has unquestionably been the most active in the history of the organization; it has therefore been a most appropriate one to mark the Association's Twentieth Anniversary and to initiate its third decade of service.

The expanded scientific program at this Annual Meeting is evident to all of you. Five scientific sessions were scheduled, as opposed to the three sessions held last year; and the program was correspondingly increased for the delegates from the Affiliate Associations.

The midyear meeting provided another impressive barometer of the Association's increasing activity: fifty-five separate functions were held in Los Angeles. It is also pertinent to note that the 1959-60 Interim Session with the Eighth Postgraduate Course, the Diabetes Program Directors' Workshop, and an Insulin Bio-assay Conference, provided the organization with a special kind of Diabetes Week activity in the area of professional education.

Membership continued to increase, though the rate of increase was somewhat slower than the Association experienced during the past few years. As many of you know, we have added two new types of corporate memberships—sustaining and contributing—as a means of according recognition to corporate benefactors that contribute substantially to the Association.

The Association's income in 1959-60 was greater than ever before—primarily due to sizable bequests which were earmarked, for the most part, for research. The extent of the organization's financial growth was dramatically impressed upon me recently. Our business manager, Mr. Erickson, and I were looking through some old financial statements about a month ago when we noted that in 1951 the total income for research was five dollars. Last year, as you probably know, the Association received $360,000 for research in a single bequest.

A Cookbook for Diabetics, by Deaconess Maude Behrman, has been published with highly successful results. The Association has already printed 50,000 copies of this 176-page book, which contains the best of the author's recipes and menus that have appeared over a twelve-year period in the ADA FORECAST. The book is now going into its third printing—to meet the general demand that has built up for it throughout the country.

A new pamphlet has been prepared for Diabetes Week in the fall. It is directed to local service clubs, and indicates ways in which these organizations can take an active part in the Diabetes Detection Drive.

Perhaps the most constructive organizational activity of the year was the questionnaire which Dr. Lukens sent to the Active Members and to which he referred last night in his remarks at the Banquet. There is no substitute for this kind of sounding of opinion, for it is fundamental to the health of any organization.

Increased organizational activity and increased expenditures and income have brought corresponding increases in administrative work and responsibility. As a result of the increased demand upon the time and energies of the national office, some projects necessarily have had to be held up. It is a pleasure to report, however, that we have started work on a new 13½ minute public education film for use on television and at meetings. It should soon be available.

The work of the national organization has been greatly advanced by the President, the Officers and Councilors, Committee Chairmen and Committee members, the Editors of our publications and, indeed, the membership at large. I am happy to express the gratitude of the staff, as well as my own appreciation for their cooperation and support.

Over the past twenty years, the American Diabetes Association has developed into a potent force in the medical and health field. With the continued expansion of its activities, the Association should make even greater advances toward achieving its broad organizational objectives in the decade ahead.

J. RICHARD CONNELLY

Recommendation by Frederick W. Williams, M.D.

In discussion of the publication of the Constitution and Bylaws and the republication of the Membership Directory, I would like to move that the general body here request the Executive Committee to reproduce in separate publications the new Constitution and Bylaws and the Membership Directory. This would let us issue the Directory as often as needed, and will not delay the printing of the Constitution and Bylaws. We just had a delay of the Directory because we are going to take two years to revise the Constitution. If we make these two separate publications, it will be better.

Dr. Lukens: I think that is a very good recommendation, Dr. Williams. I will categorically state that the Executive Committee will treat it most seriously.

Report of the Nominating Committee

The Nominating Committee is pleased to report the following slate:

As Chairman of the Committee, I would like to move that Dr. Charles H. Best, of Toronto, Canada, be elected an Honorary President by acclaim.

For President, Dr. Franklin B. Peck, Sr., of Indianapolis; for First Vice President, Dr. Blair Holcomb, of Portland, Oregon; for Second Vice President, Dr. Jerome W. Conn, of Ann Arbor; for Secretary, Dr. E. Paul Sheridan, of Denver; for Treasurer, Dr. Thomas P. Sharkey, of Dayton.

For Councilors for term ending in 1963: Dr. Thaddeus S. Danowski, of Pittsburgh; Dr. William H. Grishaw, of Beverly Hills; Dr. George J. Hamwi, of Columbus, Ohio; Dr. Henry E. Marks, of New York City; Dr. Henry E. Oppenheimer, of St. Louis; and Dr. Priscilla White, of Boston.

The Committee also recommends the election of Dr. Albert E. Renold, of Boston, to fill the unexpired term ending in 1962, which will exist with the election of Dr. Jerome W. Conn to the office of Second Vice President.

(*It was moved, seconded and voted that the nominations be closed. All nominees were duly elected.*)

FREDERICK W. WILLIAMS, M.D., *Chairman*

Installation of Incoming President

FRANCIS D. W. LUKENS, M.D., *retiring President*: The final item of business is the installation of the new President, Dr. Peck.

Dr. Peck, I want to say something that everyone here knows in the first place, but it merits repetition. It is unnecessary but a pleasure for me to remind every one of you that Dr. Peck has served this Association for twenty years on all our councils and committees with a skill and wisdom that would put him far ahead of many ex-Presidents. We could not catch up with him even if he took a vacation.

I give you this gavel, Bruce, knowing that you will carry on this Association in the finest possible style.

Remarks of Newly-installed President

Thank you, Luke.

I would like to be the first to congratulate Dr. Lukens for a most outstanding year in this Association. We have passed many landmarks. We still have many things to do. I have been admiring his relaxed posture and attitude up here. When I think of the multiplicity and magnitude of the operation of our officers, committees, and committee members, of whom there are around 300 working in the Association, I am appalled; but I am comforted by the same view of loyalty and wholehearted cooperation and friendship of everyone in this organization.

We fight in our committees, and some of us even get elected to special groups having a bad name. Dr. Paul Sheridan and I belong to one of these groups, in which there are only two members. I won't tell you the name of that organization, but it has chosen the fleur-de-lis as its emblem.

It's a lot of fun, and no matter how much we disagree we still are all working for the welfare of this great cause, the American Diabetes Association. After our fights and disagreements we are still the best friends in the world.

Thank you very much. I can't tell you how much your confidence means to me.

FRANKLIN B. PECK, SR., M.D.

9TH POSTGRADUATE COURSE JAN. 18-20, 1961

The Ninth Postgraduate Course in Diabetes and Basic Metabolic Problems will be held by the American Diabetes Association in New Orleans, Jan. 18, 19 and 20, 1961. Site of the Scientific Program will be the Louisiana State University School of Medicine, and the Jung Hotel will serve as headquarters. The complete program, including an application form, will be sent to all members in the fall. It will also be published in a forthcoming issue of DIABETES.

Features of the Course are as follows:

"Clinical Aspects of Lipids" will be the title of the day's program on Wednesday, January 18, with Faculty Members drawn primarily from the Metabolism Study Section of the National Institutes of Health, which will meet in New Orleans January 14-17.

"Diabetes as a Biological Spectrum," a panel presentation, will be held at the close of the Thursday morning session to discuss the pathogenesis and manifestations of diabetes, and the pathophysiology of the diabetic state. Panelists will be the same morning's Faculty Members.

"Seminars on Current Problems in Diabetes" will be held at the close of the Thursday afternoon session, with each Thursday Faculty Member serving as one of the leaders, using the title of his lecture as the subject of his small seminar group.

Registration Fees are $40 for Association members and $75 for nonmembers. All inquiries pertaining to the Course should be directed to the national office of the American Diabetes Association, 1 East 45th Street, New York 17, N. Y.

WINNERS OF 1959-60 GRADUATE AND MEDICAL STUDENT-INTERN ESSAY CONTEST

J. William Allgood, Charleston, South Carolina, and Phyllis Grant, M.D., Kansas City, Kansas, have been selected by the Committee on Scientific Awards of the American Diabetes Association as the winners of the 1959-60 (eighth) Graduate and Medical Student-Intern Essay Contest.

The $250 award, made possible by the St. Louis Diabetes Association, has been presented to Mr. Allgood for the best paper submitted in the field of diabetes reporting original work, whether laboratory investigation or clinical observation. Dr. Grant received the $100 prize for the best review article or case report.

Joseph R. Williamson, M.D., St. Louis, Ann M. Lawrence, Ph.D., M.D., San Francisco, Lonnie Hanauer, M.D., New York, and Jack M. Batson, M.D., Nashville, received honorable mention. Drs. Williamson and Lawrence were cited for their entries of original work; and Drs. Hanauer and Batson for their case report and review article.

Each of the above-named prize-winners and those receiving honorable mention was given a one-year subscription to Volume 9 of DIABETES.

The prize-winning paper by Mr. Allgood is entitled: "The Renal Clearance of I^{131} during the Infusion of NaI^{131} and Insulin-I^{131}." Mr. Allgood was born in 1936 in Greenville, South Carolina, and graduated from Clemson College in 1957. He is now a Senior at the Medical College of South Carolina in Charleston. He belongs to the following organizations: Society for Experimental Biology and Medicine, South Carolina Academy of Science; Phi Rho Sigma Medical Fraternity;

PHYLLIS GRANT, M.D.

J. WILLIAM ALLGOOD

Alpha Omega Alpha Scholastic Medical Society, of which he is President of the Medical College of South Carolina chapter; Student American Medical Association; Honor Council of Medical College of South Carolina. Fellowships include: Lederle Research Fellowship with Dr. Curtis Worthington, Department of Anatomy, Medical College of South Carolina (1958); National Institutes of Health Research Fellowships with Drs. John and Maria Buse, Department of Medicine, Medical College of South Carolina (1959-60). He has published "Initiation of Blanch-blush Cycles in the Mouse Uterus by Cholinergic Drugs." His present plans are to proceed to an internship and residency training in internal medicine.

"The Role of Potassium in the Therapy of Diabetic Acidosis," is the title of Dr. Grant's paper which was selected as the best in the category of review article or case report. Dr. Grant was born in New Jersey, and took her premedical work at Douglass College, New Brunswick, New Jersey, where she was graduated in 1956 with a B.A. degree. She attended Kansas University School of Medicine and received her M.D. degree in June 1960. Dr. Grant has worked in the Department of Physiology of Kansas University, and has externed at New England Hospital in Boston. She is at present interning at Wesley Hospital in Wichita. Her plans are to specialize in pediatrics.

Dr. Williamson, whose paper "Electron Microscopy of Glycogenic Changes in Beta Cells in Experimental Diabetes," won him honorable mention, was born in Enid, Oklahoma, in 1931. He received his B.A. degree from Phillips University in 1954 and his M.D. (cum laude), from Washington University in 1958. He has held the following positions: Co-Chief Resident in Pathology, Barnes Hospital; Assistant in Pathology, Washington University School of Medicine; National Cancer Institute Trainee; Trainee (N.C.I.) in Experimental Pathology; Assistant Resident in Pathology, Barnes Hospital; and Intern in Pathology, Barnes Hospital. Dr. Williamson is married and the father of two children.

Dr. Lawrence, whose paper entitled "Studies in Reproductive Physiology in the Alloxan Diabetic Female Rat: The Endocrine Basis for Impairment of Reproductive Function in Diabetes Mellitus," won honorable mention, received her B.A. from Barnard College (Columbia University) in 1952, and did graduate study at Stanford University until 1953 and at the University Laboratories of Physiology, University of Oxford, until 1954. She received a degree of Ph.D. at the Department of Anatomy, University of California at Berkeley, on studies in endocrinology. She is at present a rotating intern at the University of Chicago Clinics. She received her M.D. degree at the University of California School of Medicine in San Francisco this year. It is her intention to undertake residency training in internal medicine at the conclusion of her internship. She is married to a member of the faculty at the University of Chicago, and has a son born this April.

Dr. Hanauer, who with Dr. Batson wrote the paper entitled "Anaphylactic Shock Following Insulin Injection: Case Report and Review of the Literature," which received honorable mention, was born in New York City in 1935. He received his A.B. degree from Cornell University in 1956, and was graduated from Cornell Medical College in 1960. He is married and interning at Beth Israel Hospital in Boston.

Dr. Batson was graduated from Vanderbilt University Medical College in 1958, after completing his academic education at Vanderbilt University. He interned and was medical resident at The New York Hospital and is at the present time at Vanderbilt Hospital in Nashville completing his residency. He is married and the father of two young sons.

1960-61 GRADUATE AND MEDICAL STUDENT-INTERN ESSAY CONTESTS

Members of the American Diabetes Association and subscribers to DIABETES are asked to encourage medical students, interns, and physicians within two years after their graduation from medical school, and graduate students in the basic sciences to enter the ninth Graduate and Medical Student-Intern Essay Contests.

$250 Prize—for the best paper reporting original work, whether laboratory investigation or clinical observation.

$100 Prize—for the best review article or case report.

The prize-winners as well as those receiving honorable mention also are given a one-year's subscription to DIABETES: *The Journal of the American Diabetes Association.*

The papers will be judged on the basis of the value of the material and method of presentation. Any subject relating to diabetes and basic metabolic problems may be selected.

Papers entered in the Contest should not have been previously published. Appropriate manuscripts will be considered for publication in DIABETES.

Contestants should submit the original and two copies of their papers. Typewritten and double-spaced, all manuscripts should be mailed with a letter of transmittal by March 15, 1961, to: Committee on Scientific Awards, American Diabetes Association, Inc., 1 East 45th Street, New York 17, N. Y.

21ST ANNUAL MEETING

As previously announced, the Twenty-first Annual Meeting of the American Diabetes Association will be held in New York City, June 24-25, 1961, at the Commodore Hotel, prior to the annual session of the American Medical Association.

Physicians and other scientists who would like to present papers at the Scientific Sessions are invited to submit abstracts to Jerome W. Conn, M.D., Chairman of the Committee on Scientific Programs. Seven copies of the abstracts, which are requested in order to expedite review by the Committee, should be sent as soon as possible, but not later than March 1, 1961 to Dr. Conn in care of the national office.

The Twenty-second Annual Meeting will be held June 9-10, 1962, at the Conrad Hilton Hotel, Chicago.

1961 LILLY AWARD

Dec. 1, 1960, is the deadline for receipt of nominations for the fifth Lilly Award which will be given at the Twenty-first Annual Meeting, June 24-25, 1961, in New York City. This annual award is supported by Eli Lilly and Company and consists of $1,000 and a medal. The following stipulations govern the contest.

Purpose: To recognize demonstrated research in the field of diabetes, taking into consideration independence of thought and originality.

Eligibility: Any investigator in an appropriate field of work closely related to diabetes who is less than forty years of age on January 1 of the year in which the award is made. The research will not necessarily be judged in comparison to the work of more mature and experienced workers. The candidate should be a resident of the United States or Canada.

Nominations: Nominations for the award will be solicited from the members of the American Diabetes Association. Such nominations will be requested by repeated notices to be published in DIABETES. Names of nominees will be sent to the Chairman of the Committee on Scientific Awards and must be received before December 1 of the year preceding the award. The nomination should be accompanied by full information concerning the nominee's personality, training and research work. Six copies of each item should be submitted. No member may send in more than one nomination. A list of the nominee's publications, if any, and six copies of the publication or manuscript for which the award is to be given should also accompany the nomination. At the discretion of the Committee on Scientific Awards, the award may be given for work published during the year prior to December 1 of the year preceding the award. The nominee should be actively engaged at that time in the line of research for which the award is to be made.

Announcement: The name of the winner will be announced in the program of the Annual Meeting of the Association, and the award presented at that meeting. The winner, subject to the approval of the Committee on Scientific Programs, will be invited to present a paper on his work. Papers considered for the award must be submitted with the idea that they will be published in whole or in part in DIABETES if found acceptable to the Editor and/or Editorial Board. If the Committee should decide that no outstanding work has been presented for this consideration, the award will not be made.

Award: In addition to the monetary award and medal, traveling expenses will be given to make it possible for the recipient to receive his award in person at the Annual Meeting.

NOVEMBER 15 DEADLINE FOR RESEARCH FELLOWSHIP APPLICATIONS

The Committee on Research and Fellowships of the American Diabetes Association will award three Research Fellowships for the academic year July 1, 1961—June 30, 1962. Nov. 15, 1960, is the deadline for receipt of applications. Requests for application forms and other inquiries should be addressed to Mr. J. Richard Connelly, Executive Director, who will forward the information to the Committee.

4TH CONGRESS OF THE INTERNATIONAL DIABETES FEDERATION

A chartered plane will be available to members of the American Diabetes Association and its Affiliates who wish to attend the Fourth IDF Congress in Geneva, Switzerland, July 10-14, 1961. The plane will leave New York in the late morning of Saturday, July 8, 1961, and will stop at Boston. The fare, including the return flight four weeks later, will be somewhat less than $300. Those interested in this group transportation should communicate as soon as possible with Howard F. Root, M.D., 15 Joslin Road, Boston 15, Mass.

J. P. Hoet, M.D., Louvain, is President of the IDF and Eric Martin, M.D., Geneva, is President of the Organizing Committee of the Congress. The ADA Advisory Committee for the program includes Howard F. Root, M.D., Boston, Chairman; Alexander Marble, M.D., Boston; and Franklin B. Peck, Sr., M.D., Indianapolis.

All communications concerning the Congress should be addressed to the Secretary General, Bernard Rilliet, M.D., 4, Boulevard des Tranchees, Geneva, Switzerland.

The complete and final program of the Congress will be published in a subsequent issue of DIABETES: *The Journal of the American Diabetes Association.*

DIABETES WEEK NOVEMBER 13-19

Affiliates of the American Diabetes Association and Committees on Diabetes of County and State Medical Societies are urged to prepare final plans for their Public Education and Detection programs now, which in accordance with custom will be highlighted by Diabetes Week which immediately precedes Thanksgiving. The Organization Kit was mailed August 19, and an announcement concerning the availability of testing materials and reagents was sent out August 16. These will be followed by a Newspaper Publicity Kit and a TV-Radio Unit. Report forms will be mailed just prior to Diabetes Week.

Joseph H. Crampton, M.D., is Chairman of the Committee on Public Education and Detection.

Address your requests for information concerning available services and supplies to Mr. J. Richard Connelly, Executive Director, American Diabetes Association, Inc., 1 East 45th Street, New York 17, N. Y.

For a preview of the new Diabetes Week poster in black and white, see page A-6 of this issue of the Journal. In its original form, the poster is black, white, red and yellow.

NEW MEMBERS

The following were elected as of Aug. 1, and Sept. 1, 1960:

Active

Alabama	
Yeargan, Reagan L., Jr.	Evergreen
California	
Donnell, George N.	Los Angeles
Sherwood, Frederick	Oakland
Splitter, Stanford D.	Berkeley
District of Columbia	
Shocken, Victor	Washington
Illinois	
Bernet, Henry S.	Springfield

Indiana	
Gibson, David M.	Indianapolis
Kentucky	
McWhorter, Howard B.	Ashland
Massachusetts	
Field, Richard A.	Boston
Hall, William A.	Boston
Myers, James D.	Boston
Veit, Odette	Boston
Michigan	
Abramson, Lary N.	Detroit
Dulin, William E.	Kalamazoo
Minnesota	
Klimt, Christian R.	Minneapolis
Missouri	
McDermott, Alfred E.	Perryville
New Jersey	
McCormick, Robert V.	Madison
Woeltjen, Albert E.	Clifton
New York	
Bierman, Edwin L.	New York
Brener, Jacob L.	New York
Entmacher, Paul S.	New York
Rapp, Howard M.	Auburn
Rees, Roberts M.	Brooklyn
Warner, Robert C.	Brooklyn
Oregon	
Casterline, Ray L.	Medford
Pennsylvania	
Gentile, Anthony J.	Scranton
Green, Mary H.	Pittsburgh
Texas	
Combes, Burton	Dallas
Lindsey, Sherman B.	Temple
Wisconsin	
Lohrenz, Francis N.	Marshfield
Other Countries	
India	
Koshy, Philipose	Vellore

NEWS OF AFFILIATE ASSOCIATIONS

The CHICAGO DIABETES ASSOCIATION will conduct its Fourth Annual Symposium on Diabetes at the Offield Auditorium, Passavant Memorial Hospital, 303 East Superior Street, on Friday, Nov. 11, 1960, beginning at 9:00 a.m. Speakers will include Prof. W. H. J. Butterfield and Peter H. Wright, M.D., of Guy's Hospital Medical School, London; Sidney Goldenberg, M.D., St. Louis; Ralph A. Reis, M.D., James B. Hurd, M.D., Marvin Cornblath, M.D., Henry T. Ricketts, M.D., Frank W. Newell, M.D., and Benjamin Spargo, M.D., all of Chicago. There will be a round-table discussion at the luncheon recess at Abbott Hall, led by various members of the Diabetes Association from the faculties of medical schools in Chicago. Registration is free for members of the Association or of the American Diabetes Association and for medical students and resident house staff members. The fee for nonmembers is $25.00. Members of the Academy of General Practice may claim hour for hour credit in Category II. Inquiries should be addressed to the Chicago Diabetes Association, 620 North Michigan Ave., Chicago 11, Ill.

The FLORIDA DIABETES ASSOCIATION will hold its Annual Meeting on Thursday and Friday, Oct. 27-28, 1960, at the Balmoral Hotel, Miami Beach, Florida. The following speakers will participate in the program: Garfield G. Duncan, M.D., Philadelphia; Alexander Marble, M.D., Boston; Roger H. Unger, M.D., Dallas; A. Gorman Hills, M.D., Miami; George F. Schmitt, Jr., M.D., Miami; and Joseph C. Shipp, M.D., Gainesville, Florida. The fee for nonmembers is $25.00; for members, $10.00. Reservations should be mailed to George F. Schmitt, M.D., 30 S. E. Eighth Street, Miami, Florida.

The MICHIGAN DIABETES ASSOCIATION will give its Fall Clinical Program on Sept. 29-30, 1960, the first day at the Statler-Hilton Hotel and the second day at the Sheraton-Cadillac Hotel, Detroit. The speaker for the evening session on Thursday, September 29, at 8 p.m., will be Sidney Goldenberg, M.D., St. Louis, on "Specific Vascular Lesions in the Diabetic." Speakers for the Friday afternoon session, beginning at 2:00 p.m., will be Robert B. Leach, M.D., Detroit, "Physiology of Diabetes"; John R. McDonald, M.D., Detroit, "Pathology of Diabetes"; Henry T. Ricketts, M.D., Chicago, "Modern Insulin Therapy"; James M. Moss, M.D., Washington, D.C., "Oral Drugs in Diabetes"; and Fred W. Whitehouse, M.D., Detroit, "Clinical Use of Glucagon." A Panel Discussion on "Peripheral Vascular Disease in the Diabetic," moderated by Walter L. Anderson, M.D., Detroit, will conclude the program. Panel members will be: Dr. Ricketts, Eugene A. Osius, M.D., Detroit, Melvin A. Block, M.D., Detroit, and Dr. Goldenberg. George C. Thosteson, M.D., Detroit, will preside over the Thursday Session; Ralph L. Fitts, M.D., Grand Rapids, over the Friday Session.

The NEW JERSEY DIABETES ASSOCIATION, in cooperation with the New Jersey State Department of Health, will present its Eighth Annual Symposium on Oct. 26, 1960, at the U. S. Veterans Administration Hospital, Lyons, New Jersey. The subject will be "Research in Diabetes."

Speakers include Yale J. Topper, M.D., of the National Institutes of Health, on "Basic Laboratory Technics in Diabetes Research: A Historical Review"; Alexander Marble, M.D., Boston, on "Research Technics in the Detection of Latent Diabetes"; and Albert F. Debons, M.D., of the Brookhaven National Laboratory, on "Some Recent Studies in Lipid Metabolism and Nutrition." F. D. W. Lukens, M.D., Philadelphia, will moderate a panel discussion.

The NEW YORK DIABETES ASSOCIATION will hold its Eighth All-day Symposium entitled "Genetic Aspects of Diabetes Mellitus and Prediabetes and the Evaluation of Diagnostic Tests" on Friday, Nov. 11, 1960, at The Hotel New Yorker in New York City.

The morning session, from 9:00 a.m. to 12:00 noon, will deal with genetic aspects of diabetes mellitus. Papers will include "Inborn Errors of Carbohydrate Metabolism," by David-Yi-Young Hsia, M.D., Evanston, Illinois; "Heredity in Diabetes Mellitus," by Arthur G. Steinberg, Ph.D., Cleveland; and "Spontaneous Diabetes in Animals," by George Yerganian, Ph.D., Boston. Henry T. Ricketts, M.D., Chicago, will be dis-

cussant of the above-named papers. A special lecture entitled "The Infant of the Diabetic Mother," by Sidney Gellis, M.D., Boston, with Alfred E. Fischer, M.D., New York, as discussant, will conclude the morning session.

The afternoon session, entitled "Clinical Panel on Prediabetes and Evaluation of Diagnostic Tests," moderated by Dr. Ricketts, will begin at 2:00 p.m. The following papers will be presented: "The Rapid Intravenous Glucose Tolerance Test in Pregnancy," by Felix A. Silverstone, M.D., Edward Solomon, M.D., Jeanette Rubricine, M.D., New York; "Modification and Calibration of the Cortisone Glucose Tolerance Test in Human Volunteers," by Christian R. Klimt, M.D., Minneapolis; "Drug Responsive Tests," by Roger Unger, M.D., Dallas; and "Hormonal Influenced Tests," by Kelly M. West, M.D., Oklahoma City. A Panel Discussion including Martin G. Goldner, M.D., New York, and Irving Graef, M.D., New York, in addition to the above speakers, will conclude the afternoon program. That same evening, the Annual Banquet will be held at 8:00 p.m. Jay Tepperman, M.D., Upstate Medical Center, State University of New York College of Medicine, Syracuse, will be the after-dinner speaker. His subject: "Some Explorers of Inner Space."

Physicians, medical students and other professional personnel interested in diabetes are invited to attend this program. Advance registration is required and may be made by calling or writing the New York Diabetes Association, 104 East 40th St., New York 16, N. Y. Admission will be by ticket only. There is no registration fee.

NEWS NOTES

IMMUNO-ASSAY WORKSHOP

A two-day workshop on "The Determination of Plasma Insulin by Immuno-assay Technics" will be conducted at the Veterans Administration Hospital, 130 W. Kingsbridge Road, Bronx 68, N. Y., Oct. 20-21, 1960, under the direction of Rosalyn S. Yalow, Ph.D., and Solomon A. Berson, M.D. Those wishing to participate should make arrangements in advance.

NUTRITION EDUCATION SYMPOSIUM

A one-day Institute on Nutritional and Metabolic Considerations in Disease will be held by the Committee on Nutrition and Metabolism of the Philadelphia County Medical Society, in cooperation with the American College of Gastroenterology and the National Vitamin Foundation, on Oct. 29, 1960, at the Bellevue Stratford Hotel, Philadelphia.

The morning symposium will be moderated by Michael G. Wohl, M.D., Philadelphia. Panel speakers will include: Garfield G. Duncan, M.D., Philadelphia, "Principles of Dietotherapy"; Harold M. Mitowsky, M.D., Baltimore, "Sprue Syndrome"; Robert G. Ravdin, M.D., Philadelphia, "The Role of Nutrition in the Pre- and Postoperative Care of the Surgical Patient"; and Edward G. Reisner, Jr., M.D., New York, "Vitamin B_{12} and Folic Acid in Medicine."

The afternoon session will be moderated by Robert S. Goodhart, M.D., New York. Panel speakers will be Robert E. Olson, M.D., Pittsburgh, "Nutrition in Relation to Coronary Artery Disease"; Herbert Pollack, M.D., New York, "Obesity"; and William H. Sebrell, Jr., M.D., New York, "Vitamins in the Practice of Medicine."

The Institute is approved for four hours of Category II credit by the American Academy of General Practice.

ORAL THERAPY CONFERENCE

Recent advances in oral therapy for diabetes will be discussed by four guest lecturers November 9 at a postgraduate conference at the University of Oklahoma Medical Center.

Speakers will be: Garfield G. Duncan, M.D., Philadelphia; Henry T. Ricketts, M.D., Chicago; Stefan S. Fajans, M.D., Ann Arbor; and Leonard L. Madison, M.D., Dallas. Late research developments will be reviewed during a morning session. A short course on the present status of these oral agents in clinical practice will be held during the afternoon and evening.

Reservations may be made through the Postgraduate Office at the Medical Center, 800 NE 13, Oklahoma City, Okla.

BRITISH DIABETIC ASSOCIATION SECTION MEETINGS

The newly formed Medical and Scientific Section of The British Diabetic Association will hold a meeting in Glasgow, Scotland, Oct. 14-15, 1960. A meeting in London in the spring of 1961 is also being arranged, at which the Annual Banting Memorial Lecture of The British Diabetic Association will be given. Members of the American Diabetes Association are invited to attend the Section's meetings.

SEMINAR ON HOLIDAYS FOR CHILDREN

A seminar on "The Problem of Vacations for Children with Chronic Diseases" was held under the sponsorship of the International Children's Centre in Paris, France, June 1-3, 1960. Members of the American Diabetes Association who participated were George M. Guest, M.D., Cincinnati, who spoke on "Study of Problems Created by Holidays in Relation to Diabetics," and Henri Lestradet, M.D., Paris, "The Place of Holidays in the Life of Children with Chronic Diseases."

WESSON FUND

Wesson Fund grants totaling $100,000 a year are available to nonprofit research centers at universities, hospitals and laboratories, as well as to private individuals whose primary work is in nutritional research. Grants of $10,000 each have recently been given to Laurance W. Kinsell, M.D., Director of the Institute for Metabolic Research at Highland-Alameda County Hospital, Oakland, California; and to Theodore B. Van Itallie, M.D., Director of Medicine at St. Luke's Hospital, New York, and Associate Clinical Professor of Medicine with the Department of Nutrition at Harvard University.

Herbert Pollack, M.D., Associate Professor of Clinical Medicine at New York University, is Chairman of the Medical Advisory Board of The Wesson Fund for Medical Research and Education. Other ADA members of the Board are: Grace Goldsmith, M.D., Professor of Medicine at Tulane University, New Orleans; and Robert L. Jackson, M.D., Professor of Pediatrics, University of Missouri, Columbia, Missouri.